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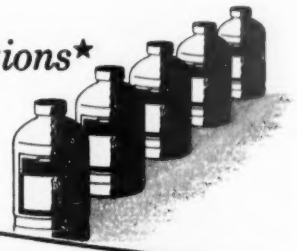

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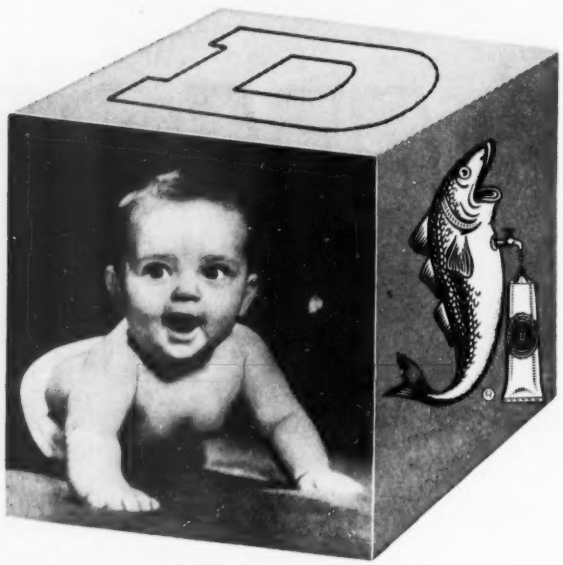


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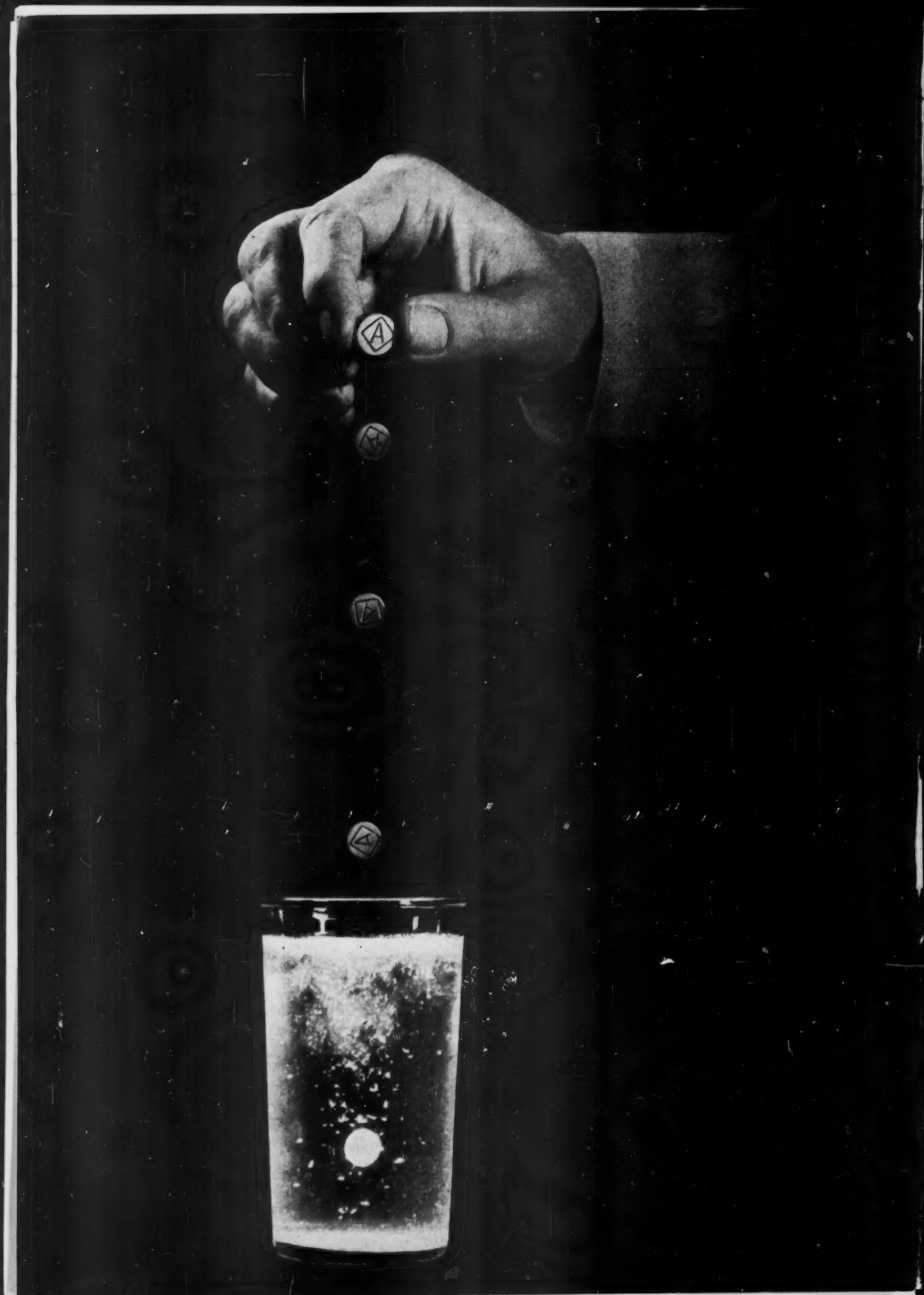

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Volume 251 DECEMBER 23, 1954 Number 26

# DIFFERENTIATION OF HYPERPARATHYROIDISM AND THE MILK-ALKALI (BURNETT) SYNDROME*

LAURENCE H. KYLE, M.D.†

WASHINGTON, D. C.

THE most recent addition to the list of hypercalcemic disorders that may stimulate hyperparathyroidism is the syndrome of excessive intake of milk and absorbable alkali. This interesting condition, first clearly delineated by Burnett and his associates[1] in 1949, is characterized especially by hypercalcemia without hypercalciuria, although several other features aid in its identification. In the five years since the original report 10 additional cases have been described, and the nature of the findings in these patients has substantiated the specific identity of the syndrome.[2-7] Recently, Carpenter and Pautler[8] described a patient who demonstrated most of the features outlined by Burnett et al.[1] but who had a parathyroid tumor. These authors suggest that the Burnett syndrome may represent primary hyperparathyroidism with atypical chemical changes resulting from excessive intake of alkali.

The 2 cases reported below illustrate the difficulties in clear-cut separation of hyperparathyroidism and the milk-alkali syndrome. Both demonstrated the characteristic features described by Burnett and his associates, and yet the basic disorders appear to have been entirely dissimilar. In 1 patient excessive intake of milk and alkali was the major problem; in the other a parathyroid adenoma was removed.

## CASE REPORTS

CASE 1. M.H. (G.U.H. 26942), a 49-year-old man, was admitted to the hospital in October, 1950, with the chief complaint of severe pruritus. This symptom had begun about 2½ years previously, when the patient incurred fractures of lumbar vertebras and was placed in a body cast for 4 months. During the period of immobilization he noticed pruritus of the back that from this time on was nearly constant. Two years before admission he became aware of small papules over the back. These were conical, approximately 4 mm. in diameter and intensely pruritic. Scratching resulted in excoriation, after which the denuded surface was replaced by a pale-gray scale. Nodules grew to 1.5 or 2 cm. and then gradually diminished in size, to be replaced by areas of pigmentation. New crops of the lesions appeared periodically, and as time went on the lesions spread to involve the remaining portions of the body, with the exception of the face. One and a half years before admission, the pruritus became so intense that the patient was unable to tolerate clothes or bed clothing and stopped all work. There was a weight loss of 30 pounds during the year before admission, and he had increasingly severe generalized muscular weakness. A large assortment of medications failed to effect relief. These included salves, ointments, lotions, antibiotics, carbon dioxide snow and x-ray therapy, as well as a number of unidentified intramuscular injections. Skin biopsy was taken, and he was subsequently informed that the skin lesions were due to nervousness. Further dermatologic opinion led to the present admission with the diagnosis of pruritus nodularis.

The past history revealed syphilitic infection 25 years before admission adequately treated on 2 occasions. Severe polydipsia and polyuria had been present for at least 18 or 20 years, with ingestion of considerable quantities of milk during this time. Six years before this study a peptic ulcer was diagnosed on radiologic examination. Since then, there had been frequent attacks of gastrointestinal pain, associated on some occasions with vomiting. Gastrointestinal symptoms were best controlled by ingestion of bicarbonate of soda (average of 226 gm. a day) and milk in amounts of 2 or 3 liters a day.

Physical examination revealed a tense man who appeared chronically ill and scratched intensely throughout the examination. He was diffusely pigmented, and over the entire body, with the exception of the face, there were numerous nodular lesions. The blood pressure was normal. The liver edge was palpable 2 cm. beneath the right costal margin. Examination was otherwise not remarkable.

Repeated urine examinations showed specific gravities ranging between 1.005 and 1.011, pH between 7 and 7.5, ++ to +++ tests for albumin and a normal sediment. The hematocrit was 25 per cent, the hemoglobin 8.3 gm. per 100 cc., and the red-cell count 2,900,000. The white-cell count was slightly elevated, with a normal differential. Studies of the blood and urine during the hospital course are summarized in Table 1. There was marked azotemia, elevation of blood bicarbonate, hypercalcemia and hyperphosphatemia. The serum albumin was 4.3 and the globulin 2.1 gm. per 100 cc. The urine concentration failed to increase after dehydration or the administration of Pitressin. A phenolsulfonphthalein test on 2 occasions demonstrated no excretion of dye. Liver-function studies were negative, as was the glucose tolerance test. The bone-marrow picture was consistent with the anemia of uremia. The excretion of calcium in the urine (Table 1) was within normal limits.

X-ray studies of the orbits, with the technic of Fleischner and Shalek,[9] disclosed bilateral annular calcification. On barium-swallow examination there was no evidence of a local tumor mass. A film of the chest was normal. A film of the kidneys showed no calculi in the urinary tract, and intravenous pyelography demonstrated no filling. Retrograde pyelograms revealed unilateral hydronephrosis. Skull films indicated slight increased density of the base, but other bone films were normal.

*From the Department of Medicine, Georgetown University School of Medicine and Georgetown University Hospital.

Supported by a grant from the William Wade Hinshaw Cancer Research Fund.

†Associate professor of medicine, Georgetown University School of Medicine.

During the early portion of the hospital course calcium was administered intravenously for the pruritus. This was discontinued when the observation of alkalosis in conjunction with severe uremia led to a complete dietary history and a tentative diagnosis of the milk-alkali syndrome. Pruritus continued without relief. Additional studies disclosed alpha-hemolytic streptococci in the bladder urine whereas cultures of both right and left ureters were negative. A skin biopsy was reported as showing hyperkeratosis. Treatment with increased fluid ingestion and a low-calcium, acid-ash diet resulted in some decrease in nonprotein nitrogen and carbon dioxide combining power. The serum calcium fell to normal levels, and there was a slight lowering of serum phosphorus concentration. Because of lack of relief from pruritus, the patient insisted on leaving the hospital.

horseshoe kidney, fused at the lower poles, with marked hydronephrosis, extremely severe nephrocalcinosis and diffuse interstitial nephritis, apparently secondary to the calcinosis; the lumens of the renal tubules had many calcium plugs and showed the inflammatory changes of acute pyelonephritis. Metastatic calcification was demonstrable in the dura, lungs, orbits, medium-sized arteries, an adrenocortical adenoma, a liver nodule and, particularly, the kidney.

Examination of the skull demonstrated thinning of the trabeculae and severe fibrosis of the marrow, suggestive of fibrous dysplasia. A large ulcer crater was present in the first portion of the duodenum. The parathyroid glands were not found after diligent dissection of the neck.

CASE 2. J.L. (G.U.H. 35522), a 42-year-old man, was admitted to the hospital in October, 1951, with the major

TABLE 1. *Studies of the Blood and Urine.*

| SOURCE OF DATA | BLOOD | | | | | | | URINE | |
|---|---|---|---|---|---|---|---|---|---|
| | CALCIUM | PHOSPHORUS | PHOSPHATASE | CARBON DIOXIDE | CHLORIDE | NONPROTEIN NITROGEN | pH | 24-HR. CALCIUM | ALBUMIN |
| | *mg./100 cc.* | *mg./100 cc.* | *Bodansky units* | *milliequiv./liter* | *milliequiv./liter* | *mg./100 cc.* | | *mg.* | |
| **Case 1:** | | | | | | | | | |
| 1st admission | 12.1 | 11.4 | 4.4 | 32 | 99 | 132 | 7.5 | — | +++ |
| | 11.4 | 10.8 | — | 26 | | 124 | 7.0 | 110 | — |
| | 9.9 | 10.0 | — | 26 | | 106 | — | 75 | — |
| | 9.4 | 10.7 | 3.6 | — | | | 5.0 | 38 | — |
| 2d admission | 7.5 | 23.0 | 22.0 | 20 | 85 | 291 | 5.5 | — | ++++ |
| | 7.5 | 23.3 | — | 16 | 81 | 385 | 4.8 | — | ++++ |
| Case 2: | | | | | | | | | |
| 1st admission | 15.0 | 5.1 | 5.3 | 42 | 73 | 42 | 7.5 | 165 | + |
| | 14.9 | 4.2 | — | 42 | 85 | 43 | — | — | + |
| | — | — | — | 30 | 97 | — | 7.0 | 86 | + |
| | 11.3 | 2.2 | — | — | — | — | — | 122 | 0 |
| 2d admission | — | — | — | 41.5 | 70 | 59 | | | |
| | 14.2 | 3.7 | — | 43 | 85 | — | 7.5 | 103 | + |
| | 13.2 | 3.3 | — | 32 | 90 | 58 | | | |
| 3d admission | 11.5 | 3.2 | 6.5 | 26 | 105 | 42 | 6.0 | 202 | 0 |
| | 11.5 | 2.5 | — | — | — | — | — | 262 | 0 |
| After operation | 10.8 | 5.04 | — | — | — | 38 | | | |

He was readmitted to the hospital on February 7, 1951, obviously both acutely and chronically ill, and still having extremely severe pruritus. After his previous discharge he had sought medical care in another hospital, where again no relief was obtained. He began to have frequent attacks of vomiting. Some diarrhea and a generalized aching, said to be deep in the bones, had occurred. Increasing weakness and progression of the diarrhea led to his second admission.

On urinalysis the pH ranged from 4.5 to 6, the specific gravity was fixed, and tests for albumin were persistently ++++. Microscopical examination of the urinary sediment disclosed a slight increase in red cells on 2 occasions. The blood nonprotein nitrogen had risen considerably; the carbon dioxide combining power was in the acidotic range, and examination of the blood now showed hypocalcemia, with striking elevation of serum phosphorus (Table 1). The alkaline phosphatase, which had been normal on the 1st admission, was 22 Bodansky units. An electrocardiogram was within normal limits. The patient was treated with increased fluids, but his condition steadily worsened and he died on the 8th hospital day.

The significant post-mortem findings included a congenital

complaints of abdominal pain and vomiting. Approximately 17 years previously he 1st experienced pain in the back and left lower quadrant, with radiation to the testicles. This pain, which was sharp and associated with nausea and vomiting, was not accompanied by dysuria, hematuria or other urinary symptoms. Hospital study was unrevealing, but shortly thereafter the patient passed a urinary calculus. For the next 3 years he felt well, but at the end of that time had a similar episode and passed another stone. From that time on he had several attacks of back pain and, at times, abdominal pain associated with nausea and vomiting. Stones were passed again on at least 2 occasions. In the year immediately before this admission he had a severe attack associated with frequency and then with oliguria. Two successive operations were performed, with removal of stones from both kidneys. Subsequently, he had almost constant left-lower-quadrant pain, increasing polyuria and nocturia, together with intermittent episodes of hematuria. During the week preceding hospitalization the symptoms increased in severity and again were associated with nausea and vomiting.

The past history revealed no fractures or other type of

bone disease. He had always been extremely fond of milk, ingesting between 1 and 2 liters a day since childhood with an even greater intake during the frequent episodes of abdominal pain in the past 15 years. Approximately 20 years before admission and 3 years before the 1st evidence of renal calculi he began to suffer from chronic indigestion, for which he took large amounts of bicarbonate of soda and 2 or 3 packages each day of a proprietary preparation ("Tums") containing calcium and magnesium carbonate. The excessive intake of alkali was continued until the time of admission. He had long been nervous and quite irritable — symptoms that he attributed to his work as a hairdresser. A single attack of pleurisy had occurred about 16 years previously without complications. There had been some slight dyspnea on exertion for several years. The family history was noncontributory.

Physical examination showed a normally developed and well nourished, nervous and impatient man. There were a few scattered, excoriated, crusted lesions on the skin, which he attributed to scratching. The eyes were slightly reddened, but an ophthalmologic consultant saw no calcification on slit-lamp examination. There was diffuse tenderness in the lower abdomen, especially in the left lower quadrant. The scars of the previous operations were well healed. Rectal examination was negative.

Urinalysis disclosed a pH of 7 to 7.5, specific gravity between 1.005 and 1.009 and a + test for albumin, with increased white cells in the sediment on 1 occasion. The hematocrit was 43 per cent, and the hemoglobin 14 gm. per 100 cc. The white-cell count and differential were normal. The total protein was 7.6 gm. per 100 cc., the albumin being 4.3 and the globulin 3.3 gm. per 100 cc. The significant chemical determinations during the hospital course are summarized in Table 1. There was considerable hypercalcemia, slight elevation of serum phosphorus, normal alkaline phosphatase, alkalosis associated with hypochloremia and moderate azotemia. X-ray examination showed bilateral renal calculi and diffuse renal calcinosis. A gastrointestinal series gave no evidence of ulcer. X-ray examination of the orbits demonstrated no calcification. Phenolsulfonphthalein excretion was 15 per cent in 15 minutes and totaled 24 per cent in 2 hours. The specific gravity of the urine was only 1.010 after overnight dehydration. Urine culture revealed gram-negative rods, sensitive to chlortetracycline and oxytetracycline and extremely sensitive to chloramphenicol. Urinary calcium excretion (Table 1) was normal.

The patient was placed on a low-calcium diet and treated with intravenous infusions of fluids. The vomiting ceased, and the carbon dioxide combining power and serum chloride concentrations returned toward normal. Chloramphenicol was administered for the urinary-tract infection.

The initial diagnosis rested between hyperparathyroidism and the milk-alkali syndrome. The presence of a normal urinary calcium excretion in the face of hypercalcemia and the lowering of the serum calcium after the institution of a low-calcium intake threw more weight behind the latter diagnosis. However, a calcium infusion was associated with changes similar to those described in patients with hyperparathyroidism,[10,11] and the serum phosphorus decreased to subnormal levels during the period of hospitalization. Consequently, the patient was discharged on a low-calcium, acid-ash diet to return for further study.

He was readmitted to the hospital 2 weeks later. After discharge he had continued to suffer with abdominal pain and vomiting together with a steady loss of weight, which approximated 18 pounds. He admitted that he had continued to take alkali in large amounts. As shown in Table 1, the chemical findings were identical with those observed previously — namely, hypercalcemia, alkalosis, an alkaline urine and normal urinary calcium excretion. Again, great symptomatic and chemical improvement followed the intravenous administration of fluids.

The patient was admitted to the hospital for the 3d time in February, 1952. After discharge his condition had stabilized. With continuation of a low-calcium, acid-ash diet there was no recurrence of nausea or vomiting, and minimal abdominal pain. The only symptom during this interval was persistent but mild pain in the flank. Blood studies revealed lack of alkalosis, definite hypercalcemia and slight lowering of serum phosphorus concentration. The urinary calcium was now significantly elevated (these and other urinary calcium studies were conducted when the patient was on a diet containing approximately 150 mg. of calcium a day). A calcium infusion test again showed the response that has been observed in hyperparathyroidism — that is, increase in 24-hour urinary excretion of phosphorus on the day of infusion, with a minimal rise in serum phosphorus.

Parathyroid exploration was consequently performed. Three apparently normal parathyroid glands were identified, but the right inferior parathyroid gland appeared to be about 3½ times the normal size. This enlarged gland was removed, and a biopsy taken of parathyroid tissue on the left. Microscopical examination of the biopsied gland showed apparently normal cellular structure, with a moderate increase in fat. The enlarged gland proved to be an adenoma of a mixed type, with a predominance of large, water-clear cells. One month after operation the serum calcium was 10.8, and the phosphorus 5.0 mg. per 100 cc. The patient continued to have mild flank pain but was free of nausea and vomiting. When last seen in August, 1952, he felt much better, though suffering with occasional hematuria. The gastrointestinal symptoms had almost entirely disappeared and he was much less nervous and irritable.

## Discussion

The first observation that hypercalcemia might complicate the therapy of peptic ulcer was made by Cope[12] in 1936. This author described 4 patients in whom alkalosis and azotemia complicated by significant elevation of serum calcium and magnesium levels developed during the ingestion of alkaline powders containing large amounts of calcium and magnesium. The serum calcium level rapidly returned to normal after medication was stopped, and consequently the possibility of hyperparathyroidism was not considered.

In their report Burnett and his associates[1] stressed the fact that their chronically hypercalcemic patients showed many features of primary hyperparathyroidism, but that certain characteristics were helpful in establishing the proper diagnosis. These included a history of prolonged intake of milk and absorbable alkali, lack of hypercalciuria or hypophosphatemia, freedom from bone disease, renal insufficiency, mild alkalosis, calcinosis and improvement on a diet low in milk and alkali. Although they stated that no one of these atypical features excluded hyperparathyroidism, they believed that the over-all picture could not be explained by this disorder. The data reported here demonstrate the fact that the characteristic features of the milk-alkali syndrome may occur in hyperparathyroidism (Table 2). Analysis of these features thus seems pertinent to this discussion.

### History of Prolonged and Excessive Intake of Milk and Alkali

Presumably the basic cause of the hypercalcemia and renal failure, this is obviously a *sine qua non* of the Burnett syndrome. The observations of Cope[12] indicate that the high-calcium content of milk is the prime cause of the hypercalcemia, and thus ingestion of excessive calcium in any form, together with alkali, may produce the syndrome. Although such an abnormal dietary intake is necessary for consideration of the milk-alkali syndrome, this history is of no value in ruling out hyperparathyroidism. The frequency of peptic ulcer in this disease, as well as the presence of ulcer symptoms in an even larger number

of patients, encourages self-medication with antiulcer therapy.[13] Case 2 fully illustrates this fact.

#### Hypercalcemia without Increased Urinary Calcium Excretion

Unusual in hyperparathyroidism this pattern is ordinarily attributed to some degree of renal impairment. If a patient with hyperparathyroidism manifested azotemia of the degree seen in the Burnett syndrome, lack of hypercalciuria would have minimal significance. Furthermore, it is possible that alkalosis per se interferes with urinary excretion of calcium.

#### Depression of Serum Phosphorus

The absence of this sign has little diagnostic value. In hyperparathyroidism with renal failure of the degree seen in the milk-alkali syndrome, serum phosphorus concentration should be increased or at least well within the normal range.

#### Skeletal Involvement

Absence of skeletal involvement or of its enzymatic manifestation, elevation of alkaline phosphatase, is of no help in differential diagnosis. It has been observed that the high-calcium (or high-phosphorus) intake of heavy milk drinkers prevents the skeletal changes of hyperparathyroidism.[14] Thus, demonstrable bone disease or even increased phosphatase activity would be most unexpected in any patient with hyperparathyroidism who drinks enough milk to suggest the presence of the milk-alkali syndrome.

#### Renal Failure with Azotemia

This finding is obviously not of real diagnostic value. Although an integral part of the milk-alkali syndrome, the uremic picture is indistinguishable from that which may occur in hyperparathyroidism, especially if calcium intake is maintained at a high level and the patient ingests alkali.

#### Calcinosis

Calcinosis, particularly the band keratopathy described by Walsh and Howard[15] and by Cogan, Albright and Bartter,[16] is not peculiar to the Burnett syndrome. It has been reported in hyperparathyroidism and vitamin D poisoning and could readily occur in any type of hypercalcemia. On the other hand, the presence of ocular calcification in nearly all the reported cases of the milk-alkali syndrome indicates that absence of this type of calcinosis should favor the existence of some other variety of hypercalcemia.

#### Mild Alkalosis

This is probably the most striking chemical feature of the milk-alkali syndrome. Actually, even normal or slightly depressed serum bicarbonate is significant considering the severe degree of acidosis usually seen in azotemia of the degree occurring in these patients. Consequently, demonstration of a normal or elevated carbon dioxide combining power in any subject with azotemia should immediately arouse suspicion of the presence of the milk-alkali syndrome. This unexpected finding led to dietary review and thence to correct clinical appraisal in Case 1. On the other hand, the same electrolyte pattern can occur in the renal failure of hyperparathyroidism if the patient is on an ulcer regimen, as in Case 2.

TABLE 2. *Comparison of Findings in Cases 1 and 2 with Those Reported by Burnett et al.*[1]

| Source of Data | Excessive Intake of Milk & Alkali | Serum Calcium | Urinary Calcium Excretion | Serum Phosphorus | Alkaline Phosphatase | Nonprotein Nitrogen | Carbon Dioxide | Calcinosis | Improvement with Dietary Correction |
|---|---|---|---|---|---|---|---|---|---|
| | | *mg./100 cc.* | *mg./day* | *mg./100 cc.* | *Bodansky units* | *mg./100 cc.* | *milli-equiv./liter* | | |
| Cases of Burnett et al.[1] | Yes | (Elevated) | (Normal) | (Not decreased) | (Normal) | (Elevated) | (Elevated) | Present | Yes |
| Case 1 | Yes | 11.4 - 12.1 | 110 | 10.8 - 11.4 | 4.4 | 124 - 132 | 26 - 32 | + + + + | Slight |
| Case 2 | Yes | 14.2 - 15.0 | 36 - 165 | 3.3 - 5.1 | 5.3 | 42 - 59 | 32 - 43 | + + + | Yes |

#### Improvement on Diet Low in Calcium and Absorbable Alkali

This is the sole differential diagnostic feature worthy of emphasis. Cases of the milk-alkali syndrome that have not progressed to the point of irreversible renal failure should show reversal of the abnormal laboratory features after dietary correction. Patients with hyperparathyroidism should demonstrate sufficient improvement in renal function to uncover the characteristic laboratory features of this disease. If, however, irreversible renal damage has occurred, differentiation of these two disorders may depend on surgical exploration and examination of the parathyroid tissue.

The data reported here, in accord with those of Burnett and his associates,[1] indicate that no single feature of the milk-alkali syndrome is completely dependable in ruling out hyperparathyroidism. Findings in the patient with hyperparathyroidism (Case 2), however, do not support the opinion that these features are diagnostic even when taken as a group. Only the sequence of change that follows correction of the abnormal diet is truly helpful, and in some cases diagnosis may depend on surgical exploration. On the other hand, I cannot subscribe to the opinion expressed by Carpenter and Pautler,[8] who apparently doubt the identity of the syndrome under discussion.

That their patient had hyperparathyroidism seems indisputable, but the patient failed to demonstrate two of the cardinal features of the milk-alkali syndrome: there was no excessive intake of alkali, and the patient had acidosis rather than alkalosis. These two facts alone would militate against serious consideration of the Burnett syndrome.

It is entirely possible that some patients considered to have hypercalcemia caused by milk and alkali ingestion may actually suffer from hyperparathyroidism. The former diagnosis was entertained strongly in Case 2, correct opinion requiring prolonged observation and the application of a special diagnostic technic. Two of the patients discussed by Burnett et al.[1] (Cases 2 and 5) demonstrated significant depression of serum phosphorus after recovery from alkalosis, and in neither was mention made of administration of any medication, such as aluminum hydroxide, that might have caused depression of serum phosphorus. Hyperparathyroidism could not be completely ruled out in Case 1 reported above, and the failure to demonstrate parathyroid tissue at post-mortem examination in this patient was extremely disturbing. Although persistent hypercalcemia could induce a certain degree of compensatory atrophy of parathyroid tissue, suppression of activity to the point of disappearance of gross structure appears most improbable. There remains only the faint consolation that no parathyroid tissue was found at autopsy in 1 of the cases in the original report.[1]

Burnett and his associates[1] noted several other features that deserve brief mention. Pruritus, the dominant symptom in Case 1 reported above, was present in 4 of the 6 original cases and has been mentioned in 8 of the 16 reported cases of hypercalcemia associated with excessive intake of milk and alkali. One patient had cutaneous nodules similar to those observed in the case reported above. It is interesting that 2 of the 10 hypercalcemic patients with vitamin D poisoning described by Howard and Meyer[17] were noted to have pruritus.

Pigmentation of the skin was present in 2 of Burnett's cases, though it was possibly of racial origin in 1, and was sufficiently striking in Case 1, reported above, to suggest Addison's disease. This manifestation has been mentioned in other patients with alkalosis. Recently, Cheyne and Whitehead[18] described a patient with azotemia who was believed to have salt-losing nephritis on the basis of excessive alkali intake, and cited 2 other reports that had a similar relation. All 3 patients showed a diffuse tanning of the skin. The patient of Cheyne and Whitehead had several features suggestive of the milk-alkali syndrome, but no mineral studies were reported. The patient described by Sawyer and Solez[19] as having salt-losing nephritis simulating adrenocortical insufficiency had a long history of excessive milk and alkali ingestion, renal failure and tanning of the skin. Although post-mortem study disclosed extensive calcinosis, no mention was made of calcium or phosphorus determinations. The third patient, summarized briefly in a review article under the heading of salt-losing nephritis, had renal failure associated with several years of alkali therapy.[20] Here, again, no consideration appears to have been given to a disturbance in calcium metabolism. On the basis of the clinical picture, which includes renal failure and tanning of the skin after prolonged alkali ingestion, and the finding of marked calcinosis at autopsy, it appears possible that one or more of these patients had a disorder similar to that reported by Burnett and his co-workers.[1]

Burnett et al.[1] mentioned hyperproteinemia as an unexpected finding in some of their patients. In the cases reported above, protein determinations were of no assistance. The patient with the presumed milk-alkali syndrome had low serum proteins, whereas the one with hyperparathyroidism showed moderate hyperproteinemia.

Abnormality of bones was detected in 2 of the cases of Burnett and his associates[1] — dense cancellous bone on microscopical examination in 1 and radiologic demonstration of extensive periosteal new bone formation in the other. In Case 1 described above there was apparent osteitis fibrosa, which, in view of the terminal rise in alkaline phosphatase activity, could have resulted from the acidosis that occurred during the latter portion of the patient's illness.

The exact mechanism of the hypercalcemia that accompanies the azotemia and alkalosis induced by prolonged milk and alkali intake is unknown. That some cases of metabolic alkalosis result in severe renal insufficiency has been noted by several investigators[21-23] Although this complication may be especially frequent with antecedent renal disease,[24] considerable evidence indicates that alkalosis may be a primary cause of renal failure. Burnett, Burrows and Commons[25] believe that severe depression of renal function usually occurs with alkalotic episodes, regardless of previous renal insufficiency. The reversal of the renal picture, which resembled the syndrome of lower-nephron nephrosis, may require several months.

The known deleterious effect of increased excretion of calcium on the kidney suggests that more severe and perhaps even permanent renal insufficiency might occur in alkalosis complicated by an excessively high intake of calcium. Certainly, the hypercalcemia of vitamin D poisoning can induce renal changes.[17] The excessive calcium excretion in immobilization has been shown to cause renal impairment,[26] a factor of possible significance in Case 1. Alkalosis associated with a high-calcium intake could result in particularly severe renal damage, not only because of the coexistence of two separate nephrotoxic factors but also because of the probability that alkalosis promotes precipitation of calcium salts in the renal tubules. In view of the apparent limitation of intestinal calcium absorption, particularly in alkalosis, it seems quite unlikely that excessive calcium intake is the sole cause of renal disease. On the other hand, it seems equally

improbable that alkalosis without increased calcium absorption could result in nephrocalcinosis. Cope,[12] who was the first to describe hypercalcemia in association with an excessive intake of alkali and calcium, drew several pertinent conclusions from studies on patients receiving alkali powders containing calcium carbonate. Patients on this regimen showed no elevation of serum calcium in the absence of alkalosis, whereas 4 patients in whom alkalosis developed on the same diet demonstrated severe hypercalcemia, which abated with cessation of alkali intake. He believed that renal failure, which was due to alkalosis and not related to antecedent kidney disease, resulted in impaired calcium excretion. Consequently, enhanced intestinal absorption of calcium, resulting from an excessive intake, produced hypercalcemia. In support of this idea Cope cites the work of Hetényi and Nógrádi,[27] who found impaired calcium excretion in nephritis. Furthermore, Cope noted that a patient who was receiving a potassium salt free of calcium became alkalotic and azotemic to a degree comparable to the other patients but did not demonstrate hypercalcemia. It therefore appears that renal failure may be the result of alkalosis, irrespective of the presence or absence of antecedent renal disease. Such renal impairment could be aggravated by excessive calcium loads. The hypercalcemia seems to be the result of an excessive intake in the face of diminished renal excretion and thus not related directly to the alkalosis. On the other hand there is no absolute evidence that the milk-alkali syndrome could develop in the absence of pre-existent renal impairment. The data of Burnett et al.[1] allow no definite conclusions, and the congenital renal abnormality in Case 1 reported above suggests that renal impairment could have existed before the dietary abnormality.

## Summary and Conclusions

Two patients with a prolonged history of excessive ingestion of milk and absorbable alkali illustrate the difficulties in clear-cut separation of the milk-alkali syndrome from hyperparathyroidism. Although both patients demonstrated all the criteria for the diagnosis of dietary hypercalcemia, 1 was shown to have a parathyroid adenoma. Of the several features that suggest the presence of the milk-alkali syndrome the combination of azotemia and alkalosis is most striking. Although the response to dietary correction is most helpful in diagnosis, the presence of irreversible renal failure may necessitate histologic examination of parathyroid tissue. Both band keratopathy and pruritus occur in other hypercalcemic disorders but appear to be especially frequent in patients who ingest large amounts of milk and alkali. Available data indicate that this syndrome occurs because of renal impairment, secondary to the alkalosis, combined with increased intake and decreased excretion of calcium.

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# A SIMPLE CERVICOMEDIASTINAL EXPLORATION FOR TISSUE DIAGNOSIS OF INTRATHORACIC DISEASE

## With Comments on the Recognition of Inoperable Carcinoma of the Lung

DWIGHT E. HARKEN, M.D.,* HARRISON BLACK, M.D.,† ROY CLAUSS, M.D.,‡ AND ROBERT E. FARRAND, M.D.§

BOSTON

SINCE Daniels's[1] report (1949) on biopsy of scalene lymph nodes for the diagnosis of intrathoracic diseases, considerable interest has been manifested in the application of this technic. Others[2,3] have substantiated its usefulness. For the past three years we have employed a procedure that supplements the advantages of scalene-node biopsy by the addition of an exploration of the superior mediastinum. This procedure has been performed in cases of pulmonary disease presenting diagnostic problems. It is also used in patients having suspected or proved carcinoma of the lung to determine operability. It is emphasized that, *in none of the patients described here,* were enlarged lymph nodes demonstrated by physical examination. The availability of tissue diagnosis in approximately a third of the series and in 40 per cent of those with carcinoma of the lung indicates the value of this simple maneuver.

### TECHNIC

The procedure is generally carried out in conjunction with diagnostic bronchoscopy. The patient's position and the skin incision are those used to expose the phrenic nerve (Fig. 1). After procaine infiltration of the skin, the anterior scalene muscle and phrenic nerve are exposed by removal of the fat pad overlying this muscle along with the contained lymph nodes. The external jugular vein may be sacrificed if it interferes with the exposure. The sternocleidomastoid muscle is retracted medially, and the superior mediastinum is entered by blunt dissection through the cervical fascia (Fig. 2). The finger is inserted medially, dorsally and caudally either anterior or posterior to the subclavian artery. The trachea is next identified, and the mediastinal pleura pushed laterally so that the paratracheal lymphatic chain can be exposed. The entire dissection produces little discomfort despite the use of only small amounts of procaine.

On the left side the arch of the aorta may be palpated. On the right, the dissection may reach the right main-stem bronchus. Enlarged lymph nodes may be enucleated with the finger if they are not fixed. When a hard, fixed mass or nodes that are difficult to enucleate are encountered, a Jackson laryngoscope or lighted retractor can be introduced, and a laryngeal biopsy forceps used to obtain tissue

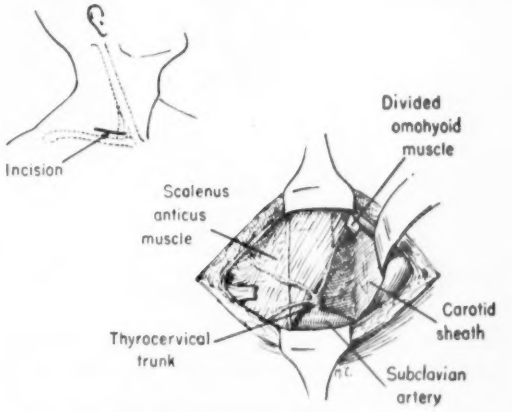


FIGURE 1. *Standard Paraclavicular Incision for Exposure of the Anterior Scalene Muscle.*
*Shown below is the anatomical appearance after excision of the fat pad.*

under direct vision (Fig. 3). Needle exploration of a pulsating mass or Silverman needle biopsy of tumors may also be carried out. If the mediastinal exploration is negative, the carotid sheath and retro-

FIGURE 2. *Superior Mediastinum Entered by Blunt Dissection Directed Mediad, Dorsad and Caudad.*

sternal areas are examined, and any suspicious nodes removed (Fig. 4).

The side elected for this exploration is based on Rouvière's[4] description (Fig. 5) of the lymphatic

*Associate clinical professor of surgery, Harvard Medical School; thoracic surgeon, Peter Bent Brigham Hospital.

†Assistant in surgery, Harvard Medical School; associate in surgery, Peter Bent Brigham Hospital.

‡Formerly, assistant resident in surgery, Peter Bent Brigham Hospital.

§Thoracic surgeon, Fitchburg, Henry Heywood and Leominster hospitals.

drainage of the human lung. With a right-sided pulmonary lesion, only the right cervicomediastinal exploration is carried out because the drainage is via the right paratracheal chain. A bilateral procedure is employed for lesions in the lower half of the left lung because of the possibility of metastases to the carinal nodes and thence up the right paratracheal chain; for lesions of the left upper lobe only the left side is explored.

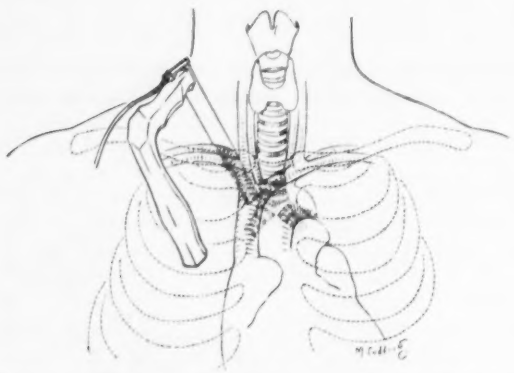

FIGURE 3. *Use of the Laryngoscope as a Lighted Retractor to Expose Upper Mediastinal Lymph Nodes.*

## COMPLICATIONS

Despite the apprehension expressed by internists and thoracic surgeons that serious complications would result from this procedure, experience with 300 operations assures us of its safety. Hemorrhage has occurred twice as the result of injury to the subclavian or internal jugular vein but has been readily controlled with Gelfoam. A pneumothorax was produced in 2 cases, but catheter aspiration through the operative site expanded the lungs as the incision was closed. Because of the excursion of the mobilized mediastinal pleura during cough or deep breathing, air may be sucked into or expressed from the incision. This should not be interpreted as evidence that a pneumothorax has been produced.

There have been no other complications.

## RESULTS

One hundred and forty-two cases are available for the analysis from June, 1950, through March, 1953 (Table 1). A positive histologic diagnosis was obtained in 45, or 31.7 per cent. The various diagnoses established and their frequency are shown in Table 2.

Among the 142 cases there were 78 in which a tissue diagnosis of bronchogenic carcinoma was possible by bronchoscopic biopsy or biopsy at the time of thoracotomy. Of these 78 patients 31, or 39.8 per cent, had metastases to the cervical or upper mediastinal lymph nodes not evident on physical examination.

## DISCUSSION

The procedure described represents an extension of the exploration used by Daniels,[1] Storey and Reynolds[2] and Shefts et al.,[3] which was limited to the lymph nodes in the pre-scalene fat pad. It seems reasonable that the superior mediastinal exploration, including the biopsy of the paratracheal lymphatic chains, should increase the yield of positive results. In this experience approximately *half the positive results came from tissue removed from the mediastinum and not the scalene fat pad.* This comment is made because Shefts and his associates reported similar percentages of positive results in their experience with removal of the pre-scalene tissue alone. It is important to note, however, that they did not state whether or not lymph nodes were palpable in their cases.

Obviously, if cases with palpable nodes are included, positive results will be more frequent. Conversely, in the presence of palpable nodes the mediastinal exploration is hardly necessary. In addition to this consideration the composition of the present series in terms of diseases encountered differed considerably from that of Shefts, Terrill and Swindell[3] and rendered strict comparison difficult. Carcinoma of the lung was common in our series, and there were few cases of bilateral parenchymal disease, whereas in that of Shefts et al.[3] Boeck's sarcoid was the most frequent diagnosis, being present in more than half the cases. The important point to remember is that the positive results in approximately half our patients were obtained only from material in the superior mediastinum. In these cases a simple scalene biopsy would not have been helpful. This experience emphasizes the value of the combined cervicomediastinal exploration for the diagnosis of pulmonary diseases.

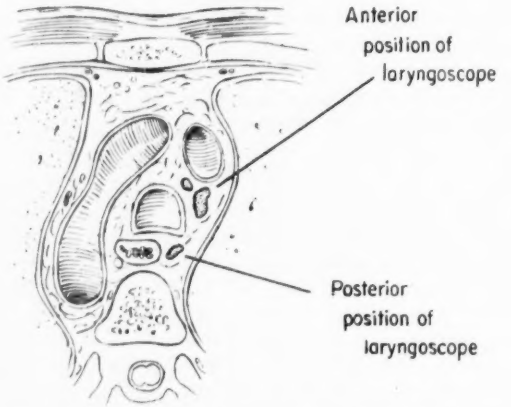


FIGURE 4. *Horizontal Body Section, Showing Position of Lymphatic Chains.*

### Carcinoma of the Lung

As experience with this diagnostic technic accumulated, it became our policy to make it part of the evaluation of all patients with known or potential carcinomas of the lung. As noted in Table 1, in approximately 40 per cent of the patients with this lesion positive nodes were recovered by this procedure. This information has produced considerable controversy over the definition of "inoperability."

It is well known that the presence of metastases in the lymph nodes removed during a pneumonectomy for carcinoma of the lung lowers the five-year salvage rate. Overholt and Schmidt[5] described a 40 per cent five-year survival rate in resected cases when the lymph nodes were negative for metastases as contrasted with one of 20 per cent when the nodes were positive. Adams[6] found 35 per cent of patients alive at the end of five years when the nodes were negative as opposed to 17 per cent when they were positive. Moore[7] reported 22 per cent alive at the end of five years when the nodes were positive but 15 per cent when they were negative. The series of Churchill et al.[8] showed the most striking difference, 34 per cent of patients with negative nodes being alive at the end of five years after resection and no survivors when there were regional-lymph-node metastases.

In all these series the diagnosis of metastasis was obviously based on the findings in the lymph nodes excised during the performance of the pneumonectomy or lobectomy. Lymph-node involvement in or close to the lung is therefore an unfavorable prognostic sign. When metastases have reached the superior mediastinum or the lower cervical region, it seems reasonable to question whether any five-year salvage can be obtained by excisional surgery.

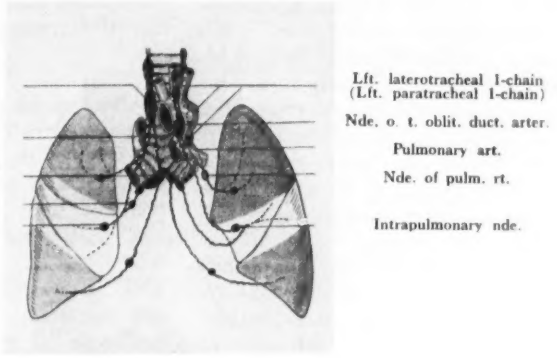
Nde. o. t. v. azygos
V. azygos
Nde. of the bifurcation (Intertracheobronch. gr.)
Inf. nde. of pulm. rt.
Intrapulmonary nde.
Lft. laterotracheal l-chain (Lft. paratracheal l-chain)
Nde. o. t. oblit. duct. arter.
Pulmonary art.
Nde. of pulm. rt.
Intrapulmonary nde.

FIGURE 5. *Diagram of the Lymphatic Drainage of the Lungs.*
*Note the crossover from the left lower lobe via carinal nodes (after Rouvière[1]).*

TABLE 1. *Frequency of Tissue Diagnosis by Cervicomediastinal Exploration.*

| TYPE | NO. OF CASES |
|---|---|
| Total available for analysis | 142 |
| Positive lymph nodes | 45(31.7%) |
| Proved cases of carcinoma of lung | 78 |
| Carcinoma of lung with metastasis to cervical or upper mediastinal lymph nodes | 31(39.8%) |

Currently, a radical block dissection of the mediastinal lymph nodes from the apex of the pleural space to the diaphragm is being carried out in many clinics. We also consider this technic indicated when thoracotomy has been elected and extirpation of the tumor appears possible. Whether the five-year survival rate in patients with metastases to the lymph nodes will be improved by such procedures remains to be seen. At least on the basis of the early reports, complications such as bleeding and bronchopleural fistula (presumably from devascularization of the bronchial stump) appear to be significantly more frequent than after simple pneumonectomy. Therefore, one must inquire whether routine radical excision of carcinoma of the lung, with the attendant higher complication and mortality, can be justified in the pursuit of potentially better survival rates for patients with metastases to the upper mediastinal and cervical lymph nodes.

TABLE 2. *Diagnoses Obtained by Cervicomediastinal Exploration in 142 Cases.*

| DIAGNOSIS | NO. OF CASES |
|---|---|
| Carcinoma of lung with metastasis | 31 |
| Sarcoid | 7 |
| Hodgkin's disease | 2 |
| Carcinoma of esophagus with metastasis | 2 |
| Granuloma compatible with tuberculosis | 2 |
| Plasmacytoma | 1 |
| Total | 45 |

To borrow a phrase from Bricker and Modlin,[9] who have applied it to the evaluation of pelvic evisceration for extensive carcinoma, one must inquire

into the "aggravation rate" as well as into the mortality rates and percentages of five-year survival. If a resection has a small chance of curing the patient and increases his likelihood of dying or of suffering from operative complications, such an operation should be avoided.

There is at least one situation in which it is proper to ask if there is not a point in the life cycle of carcinoma of the lung at which extirpative therapy becomes hopeless and constitutes a menace to the patient. Such a case is lymph-node involvement as high as the cervicomediastinal exploration reaches with an undifferentiated tumor. *A technic that spares needless suffering for the hopelessly involved patient is as important as the extension of excisional therapy in an attempt to cure more people.*

Two further points need clarification, and in these areas subjective "clinical opinion" has to take the place of definitive information that is not available at present. The first is the matter of *palliative resection*, and the second is a definition of attitude toward *radical resection* once resection has been decided on. We believe that palliative resection should be reserved for patients suffering from infection or hemorrhage. When cervicomediastinal metastases have been demonstrated, we consider the likelihood of aggravation by resection to exceed the chance of palliation. If the preoperative study does not indicate extension or other, more commonly accepted evidence of inoperability (such as tracheal invasion, distant metastases or positive pleural fluid) and the patient is subjected to the discomfort of operation we then subscribe to the policy of radical excision with block dissection of the lymphatics as vigorously as any of its proponents.

This policy of excluding from radical surgery patients with cervicomediastinal lymphatic metastases has been called defeatist. However, since the surgeon is bound to be defeated at times, it behooves one to seek critical methods of recognizing predestined defeat. If this simple and painless technic can spare some incurable patients the risk and discomfort of thoracotomy it is distinctly useful.


### Summary

A technic for the diagnosis of intrathoracic disease that combines scalene-lymph-node biopsy with exploration of the superior mediastinum is described. One hundred and forty-two such explorations are reviewed, and the results analyzed.

A positive tissue diagnosis was made in 31.7 per cent of the cases.

Of 78 proved cases of carcinoma of the lung, 31 (40 per cent) showed metastases to the superior mediastinal or cervical lymph nodes.

Finally, the implications of such metastases in the decision to use or forego surgical treatment are considered.


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# SPLENECTOMY FOR "PURE RED-CELL" HYPOPLASTIC (AREGENERATIVE) ANEMIA ASSOCIATED WITH AUTOIMMUNE HEMOLYTIC DISEASE*

## Report of a Case


GUSTAVE EISEMANN, M.D.,† AND WILLIAM DAMESHEK, M.D.‡

BOSTON


THIS report deals with an apparently unique case in which there was simultaneously selective red-cell aplasia of the bone marrow and an autoimmune hemolytic mechanism. The combination of continued lack of erythrocyte production with excessive blood destruction eventually led to the need for weekly blood transfusions, which were made increasingly difficult by thrombosed veins and the development of transfusion reactions. After a period during which there was complete absence of reticulocytes in the blood and of nucleated red cells in the marrow, splenectomy was performed. No response whatever took place for seventeen days, but on the eighteenth day, the first reticulocytes appeared in the blood simultaneously with the appearance of a large number of erythroblasts in the bone marrow. The patient then made an uneventful recovery.

Hypoplastic anemia involving only the red cells of the marrow is a rare disease, particularly in adults. Its association with an autoimmune mechanism has thus


*From the Ziskind Laboratories (Blood Research Laboratory), New England Center Hospital, and the Department of Medicine, Tufts College Medical School.



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†Formerly, research fellow in hematology, New England Center Hospital.

‡Clinical professor of medicine, Tufts College Medical School; senior physician (hematologist), New England Center Hospital; director, Blood Research Laboratory.

far not been recorded. The remarkable response to splenectomy in the present case indicates very strongly that a humoral inhibitory factor was present in the spleen, and, when it was removed, allowed the development of normal red-cell production in the marrow. The simultaneous cessation of abnormal blood destruction led to complete recovery from what was apparently a hopeless situation.

## Case Report

V.B. (N.E.C.H. 79-772), a 58-year-old housewife, had apparently been in good health until November, 1952, when she was admitted to the Mount Sinai Hospital, Miami, Florida, with bilateral thrombophlebitis of the legs. The red-cell count was 3,200,000, with a hemoglobin of 8.25 gm. per 100 cc., and the white-cell count 2350. Dicumarol was administered and then continued on an ambulatory basis.

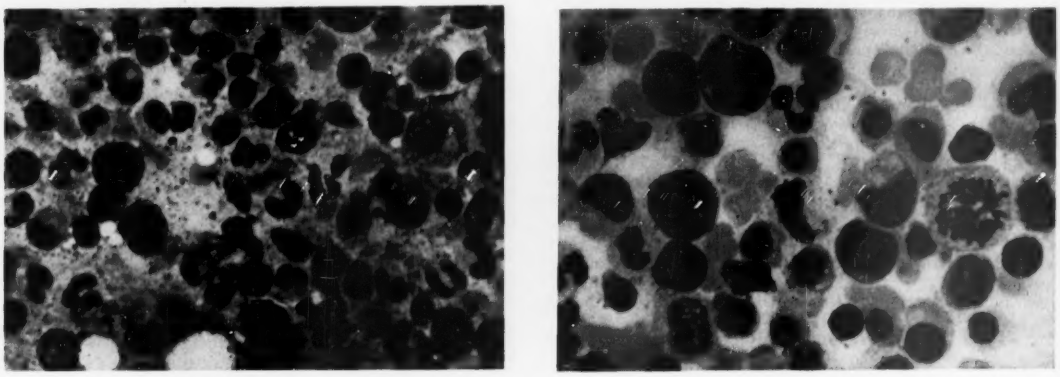
Because of progressive weakness and fatigue, the patient was readmitted to the same hospital on December 22. Physical examination revealed well defined hepatomegaly and splenomegaly, both organs extending 5 cm. below the respective costal margins. The thrombophlebitis previously present had subsided. The red-cell count was 2,600,000, and the hemoglobin 7 gm. per 100 cc. After discontinuance of Dicumarol therapy she was very weak. Examination of the blood on the 2d hospital day showed a red-cell count of 1,800,000, with a hemoglobin of 5.3 gm. per 100 cc., and a white-cell count of 3800, with 78 per cent neutrophils, 15 per cent lymphocytes, 4 per cent monocytes and 3 per cent eosinophils; platelets were 475,000 per cubic millimeter (Dameshek method). The prothrombin time was 16 seconds (control, 14 seconds). The bone marrow was reported as hypocellular; the myeloid-erythroid ratio was 12:1. The nucleated red cells were conspicuously reduced, and there was apparent maturation arrest of the erythroid cells at the normoblast A level.

August 10, 1953. Severe nonhemolytic transfusion reactions, apparently of the "plasma" type, developed, and as a result, it was necessary to give the blood as thrice-washed packed red cells.

Physical examination showed a chronically ill woman with a brownish-gray pigmentation of the skin. The liver was firm, nonnodular and palpable 12 cm. below the right costal margin. The spleen was also firm and was palpable 8 cm. below the left costal margin. There was bilateral tenderness of the calf muscles.

Examination of the blood disclosed a red-cell count of 1,900,000, with a hemoglobin of 6.2 gm. per 100 cc., a hematocrit of 24 and reticulocytes of 0.3 per cent and a platelet count of 300,000. The white-cell count was 4600, with 82 per cent neutrophils, 8 per cent lymphocytes, 5 per cent monocytes, 4 per cent eosinophils and 1 per cent basophils. Urinalysis was normal. The total serum protein was 7.3 gm. per 100 cc. (albumin of 3.5 and globulin of 3.8 gm. per 100 cc.), and the total serum bilirubin 0.8 mg. per 100 cc.; the prothrombin time was 100 per cent of normal. The serum hemoglobin, taken before arising in the morning, was 2.5 mg. per 100 cc. The L. E. test was negative. Fecal urobilinogen was 130 mg. a day. The hemolytic index was 42 (normal, about 20). Red-cell hypotonic fragility was normal. A Crosby thrombin test for paroxysmal nocturnal hemoglobinuria was + on one occasion and subsequently negative; the Ham acid hemolysis test was negative. The direct Coombs test was strongly positive. Bone-marrow aspirations were hypocellular, with an almost complete absence of erythroid cells; those that were present were interpreted as erythrogones, the "stem" cell of the red-cell series. The blood was Type A and Rh positive.

Blood transfusions were given to elevate the hemoglobin to 10 gm. per 100 cc., and cortisone was continued in a dosage of 50 mg. daily. Because of repeated attacks of severe chest pains interpreted as possible thromboses of large chest blood vessels, Danilone (2 phenyl 1, 3 indanedione) was administered in a dosage of 50 mg. daily. The prothrombin level was maintained between 10 and 20 per cent of normal. After discharge from the hospital on August 22 weekly blood



A B

Figure 1. *Bone Marrow before Splenectomy* (A), *Showing Almost Complete Absence of Erythroid Cells, and Three Weeks after Splenectomy* (B), *Showing Striking Erythroid Hyperplasia.*

The patient was given several blood transfusions, and ACTH therapy was begun. One week later multiple thromboses of veins of the arms developed, and the thrombophlebitis of the legs recurred. Heparin was administered, and cortisone substituted for ACTH. Except for a pulmonary embolism, no subsequent episode related to thrombosis occurred. During the 6 weeks in the hospital the reticulocyte level did not exceed 0.2 per cent. Cortisone, in a dosage of 50 mg. a day, was continued until September 15, 1953.

The patient was then followed on an ambulatory basis. To maintain the red-cell count at reasonably good levels of approximately 3,000,000 to 3,500,000, an average of 1 blood transfusion a week was required. Twenty transfusions of 500 cc. each were given from March 15 to the time of the 1st admission to the New England Center Hospital on transfusions were again required. However, in view of increasing difficulty in their administration because of recurrent venous thromboses and plasma transfusion reactions, the patient was again admitted to the hospital on October 5.

Examination of the blood on this admission showed a red-cell count of 2,000,000, with a hemoglobin of 5.6 gm. per 100 cc., hematocrit of 19 per cent, no visible reticulocytes and a platelet count of 402,000; the white-cell count was 7200, with a normal differential count. The Coombs test was strongly positive; liver-function studies, including bromsulfalein excretion, were negative. The serum iron was 233 microgm. per 100 cc. Another bone-marrow examination demonstrated a hypocellular marrow, with almost complete absence of erythroid cells, except for a few isolated erythrogones (Fig. 1*A*). The cells of the myeloid series and the megakaryocytes were normal.

Since all the various therapeutic maneuvers had met with failure and the readministration of ACTH was considered inadvisable on account of the possibility of further thrombotic episodes, splenectomy was decided on. It was thought that this procedure might at least diminish the transfusion requirements to some extent. No effect on red-cell production was anticipated.

In preparation for surgery, the patient was given a blood transfusion of washed, packed Type A, Rh-positive red cells. A severe reaction took place in association with the development of severe chest pain radiating to the back. The plasma hemoglobin levels did not rise above 15 mg. per 100 cc. during the next day, and there was no other evidence of a hemolytic reaction. A roentgenogram of the chest and an electrocardiogram were normal. Subsequently, only Group O, Rh-negative blood was used, and no further transfusion reactions occurred.

Splenectomy was performed on October 14. The spleen, which weighed 600 gm., showed generalized hyperplasia of normal tissue and moderate hemosiderosis. There was no appreciable erythrophagocytosis and no evidence of myeloid metaplasia. The postoperative course was complicated by the development of ileus.

Postoperatively, there was a well defined decrease in blood-transfusion requirements. Thus, in the 14 days after splenectomy, the hemoglobin dropped only 1.3 gm. per 100 cc., whereas before operation an average decrease of 2 gm. per 100 cc. a week had taken place. A bone-marrow aspiration on the 8th postoperative day again showed a complete absence of erythroid elements, with an increase in lymphocytes and the presence of large numbers of mast cells. The myeloid cells and the megakaryocytes were normal.

For 17 days after operation not a single reticulocyte was seen in the peripheral blood in counts of several thousand red cells. However, on the 18th postoperative day, 1 reticulocyte was found among 1000 red cells (0.1 per cent). These were the 1st reticulocytes found in the peripheral blood after admission 26 days previously. Examination on that day showed a hypercellular bone marrow containing numerous clusters of erythroid cells in various stages of maturation, including many normoblasts of the B and C type. Subsequently, a definite reticulocytosis developed, a peak reticulocyte response of 6.8 per cent occurring on the 28th postoperative day. On the 22d day the marrow was extremely hyperplastic with marked erythroid hyperplasia (Fig. 1*B*). To ensure good wound healing, the patient was given 2 blood transfusions immediately after operation. Before discharge from the hospital on November 14, the Coombs test was ++. Differential agglutination of the red cells showed 60 per cent to be Type O, Rh-positive or transfused cells, and 40 per cent Type A, Rh-positive or the patient's cells.

Since her return to her home she has maintained normal blood levels without further blood transfusions. The positive Coombs test has persisted, however, although in slight degree. A graphic presentation of the course is given in Figure 2.

## Discussion

"Pure red-cell" anemia is a rare form of hypoplastic anemia characterized by complete or almost complete absence of cells of the erythroid series, while cells of the granulocytic series and megakaryocytes may be present in normal number. It is most commonly found in infancy and childhood and is characterized by progressive pallor and normochromic, normocytic anemia with the complete or almost complete absence of reticulocytes. Blood transfusions to maintain normal hemoglobin levels have been the only effective therapy, and splenectomy has usually been of no value. Cortisone was effective in a single case reported by Gasser.[1]

The etiology of this rare condition is unknown. Smith,[2] in a recent review of hypoplastic anemias, described 2 cases of the "pure red-cell" type in which the hematopoietic defect may have resulted from specific fetal injury. In the first case the mother, who was Group O, Rh positive, may have developed isoimmunization against the Group A, Rh-positive cells of the fetus. The maximum anti-A serum titer was 1:128,000. In the second case the anemia occurred in an infant with a polycystic kidney. Smith postulated that the same factor that caused the maldevelop-

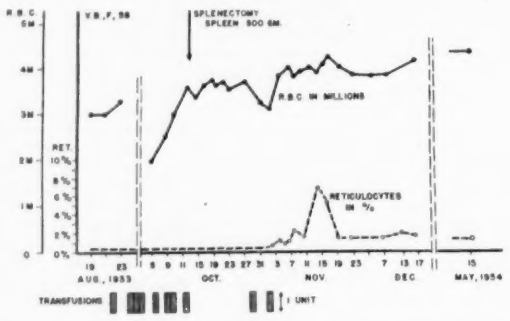



Figure 2. *Red-Cell Counts, Reticulocyte Counts and Transfusion Requirements before and after Splenectomy.*

ment in the urinary system was associated with the abnormality in erythropoiesis.

Loeb et al.[3] reported 2 cases of primary erythroid hypoplasia in adolescent boys, both of whom had complete recovery of erythropoiesis of the marrow after splenectomy. In the first case, which also responded to cortisone, there was an associated hemolytic component, although the Coombs test was negative. These 2 cases are possibly similar to those of familial hypoplastic anemia described by Estren and Dameshek.[4]

Gasser[5] observed temporary aregenerative crisis of one week's duration in 10 children with severe anemia. The bone marrow contained early erythroid cells, probably erythrogones. The etiology of these temporary crises was not clear; almost all patients had histories of frequent allergic diseases. Gasser concluded that these cases might be related to the "aplastic" or "aregenerative" crises of hereditary spherocytosis.

The first report of pure red-cell anemia in an adult was by Moeschlin and Rohr.[6] The patient, a twenty-year-old woman, was observed for three years, during which there was complete reticulocytopenia. Ross et al.[7] recently discussed 2 cases of severe red-cell aplasia and extreme reticulocytopenia associated with thymoma. Removal of the thymic tumor did not stimulate erythropoiesis in these cases, although in 4 of 7 cases recorded in the literature and reviewed by these authors,[7] temporary to permanent effects took place. Two patients showing pure red-cell anemia and thy-

moma have also been observed in our clinic. Removal of the thymoma in 1 case was without benefit. Temporary interruption of hematopoiesis of seven to twenty days' duration is known to occur in association in the hemolytic crises of hereditary spherocytosis. Owren,[8] who described "aplasia" of erythropoiesis in the latter condition postulated that the crisis was not hemolytic but due to red-cell aplasia. On the other hand Dameshek and Bloom,[9] in a study of a group of cases sharing the same findings, ascribed the crisis to two factors: marked exaggeration of the usual hemolytic mechanism and arrested maturation of red cells in the marrow induced by a humoral hypersplenic inhibitory effect. These interpretations would relate these cases to the one reported above. Singer et al.[10] presented a case of sickle-cell anemia in which aplastic crisis developed during the course of viral pneumonia.

The precipitating factor of the crisis in hereditary spherocytosis is not clear, although its occurrence in several members of one family within a few days of each other is strong evidence in favor of an infectious agent as the trigger mechanism.[9,11]

We have been unable to find any report of temporary red-cell aplasia associated with autoimmune hemolytic disease, although we have observed 2 cases in which the blood reticulocytes were relatively low and the bone marrow showed mostly primitive nucleated red cells. One of these cases has been recorded briefly.[12] Complete reticulocytopenia in association with complete lack of erythropoiesis in the marrow is thus unique in acquired autoimmune hemolytic anemia and in complete contradistinction to the usual reticulocytosis and striking erythroid hyperplasia of the disease.

#### Evaluation of the Patient

The case reported above presented many unique features. Thus, it is the first report of autoimmune hemolytic disease associated with prolonged aregenerative anemia and the first in which there was a definite indication that hypersplenism was responsible for the lack of erythropoiesis and the pure red-cell anemia. Unfortunately, the spleen was discarded before studies of the effect of splenic extract in animals could be performed.

Hypersplenism may be defined as a condition in which, in the presence of an enlarged spleen, there are single or multiple blood cytopenias in association with a normally hypercellular bone marrow. According to our own views[12] the cytopenias are the result of splenic inhibitory effects on the marrow, with consequent maturation arrest or blocked delivery of cells from the marrow to the peripheral blood. In the present case the recovery of complete bone-marrow erythropoiesis that followed splenectomy, after ten months of aregenerative anemia, strongly suggests the presence in the spleen of a factor that acted on the red-cell precursors, resulting in a complete inhibition of their maturation. The delay for more than two weeks in the appearance of any evidence of erythropoiesis after splenectomy seemed to be a further indication of a humoral factor arising in the spleen and requiring at least two weeks for removal from the circulation.

The sequence of events in this patient was, first of all, a relatively mild anemia, discovered during an attack of thrombophlebitis; on recovery from the attack of thrombophlebitis autoimmune hemolytic disease was discovered, and later there was marked erythroblastopenia of the bone marrow. The severe anemia that ensued required numerous blood transfusions. The entire clinical picture was complicated by the occurrence of multiple venous thromboses, the cause of which was not clear. Plasma transfusion reactions and severe transfusion hemosiderosis also developed. ACTH and cortisone were of no benefit. At one time the many atypical features of the case suggested to several observers the possibility of paroxysmal nocturnal hemoglobinuria, but the Ham and Crosby tests were negative, and none of the other features of the disease were present.

The fundamental mechanism responsible for the development of autoimmune hemolytic anemia is unknown, although it occurs in association with many diseases.[13] It is possible that the thrombophlebitis in the present case set off a "trigger mechanism," causing autosensitization and thus autoimmune hemolytic disease. The splenic enlargement that followed may in turn have resulted in a hypersplenic action, with a particular effect on the bone-marrow nucleated red cells. It is also possible that the specific aregenerative state of the nucleated red cells in the marrow was the result of a direct action of the incomplete erythrocyte antibodies on the red-cell precursors, with complete inhibition of erythropoiesis. The splenectomy may have removed a large source of the antibody-producing tissue, as shown by the diminution in the strength of the Coombs test.

The exact role of the spleen in relation to hematopoiesis is by no means clear. Nevertheless, the occasional striking benefit of splenectomy in various patients with hypoplastic anemia and in others with bone-marrow "failure" suggests a strong consideration of splenectomy in all patients with aregenerative anemia.

## Summary and Conclusions

A case of acquired autoimmune hemolytic disease and prolonged aregenerative or "pure red-cell" hypoplastic anemia in which there was a recovery of full erythropoiesis after splenectomy is reported. The complete absence of erythropoiesis and of reticulocytes before splenectomy and the striking erythropoiesis and complete hematologic recovery beginning two weeks after splenectomy strongly suggest a hypersplenic mechanism.

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# PNEUMOCOCCAL PNEUMONIA TREATED WITH ANTIBIOTICS*

## The Prognostic Significance of Certain Clinical Findings


THOMAS E. VAN METRE, JR., M.D.†

BALTIMORE


SINCE the introduction of antibacterial agents effective against the pneumococcus, there has been a definite decrease in mortality in pneumococcal pneumonia—from approximately 30 per cent in the era before specific treatment, to about 5 per cent in the antibiotic era.[1] Despite these improvements, however, many patients still die of the disease, and others have an unusually slow and complicated convalescence. It is important, therefore, to study clinical findings in fatal and prolonged nonfatal cases with an unfavorable outcome.

It has been well established that certain clinical findings have prognostic significance in nonspecifically treated pneumococcal pneumonia. Heffron[2] collected data from large series of such cases and showed that an increased mortality is associated with increasing age, chronic alcoholism, the presence of concomitant disease, certain types of pneumococci, bacteremia, multilobar involvement and a low white-cell count. Some of his pertinent data are shown in Table 1.

There is considerable evidence that some of these same clinical findings have an effect on mortality in antibiotic-treated lobar pneumonia,[1,3-9] Increasing age, bacteremia, severe concomitant disease, multilobar involvement and leukopenia have been shown to be associated with an increased mortality (Table 2). There has been at least the impression that Type 3 pneumococcus infections and alcoholism are associated with an increased mortality.[1]

There is less evidence that these clinical findings have prognostic significance in relation to slow recovery in nonfatal cases. McDermott and Horsfall[10] state that, despite specific antibiotic treatment, elderly people and those who are very ill with extensive pneumonia often recover slowly, with healing by fibrosis and incomplete resolution. However, this observation is undocumented, and there is little other documented evidence on this point in the literature.

The study reported here was begun to obtain more information on the effect of these clinical findings on both mortality and slow recovery in antibiotic-treated pneumococcal pneumonia.

TABLE 1. *Mortality Associated with Certain Clinical Findings in Nonspecifically Treated Pneumococcal Pneumonia.**

| FACTOR | NO. OF CASES | MORTALITY |
|---|---|---|
| | | % |
| Patients 10-20 yr. of age | 329 | 10.0 |
| Patients 60-69 yr. of age | 100 | 72.0 |
| One lobe involved | 800 | 8.5 |
| Two lobes involved | 428 | 24.5 |
| Three lobes involved | 172 | 40.7 |
| Four lobes involved | 44 | 68.2 |
| Five lobes involved | 11 | 100.0 |
| No history of alcoholism | 526 | 22.1 |
| History of chronic alcoholism | 214 | 41.5 |
| No concomitant disease | 675 | 23.9 |
| Concomitant disease | 327 | 47.4 |
| No bacteremia | 2158 | 13.3 |
| Bacteremia | 816 | 61.8 |
| White-cell count under 10,000 | 29 | 65.0 |
| White-cell count 10,000-20,000 | 143 | 23.0 |
| White-cell count 20,000-30,000 | 177 | 18.0 |
| White-cell count 30,000-40,000 | 76 | 14.4 |
| Type 1 pneumococcus | 3088 | 26.6 |
| Type 2 pneumococcus | 1753 | 37.1 |
| Type 3 pneumococcus | 1214 | 46.0 |
| Other types of pneumococcus | 1764 | 23.0 |

*Based on data of Heffron.[2]

## MATERIALS AND METHODS

The material consists of 358 cases of pneumococcal pneumonia observed at the Johns Hopkins Hospital between July, 1946, and June, 1952. The clinical diagnosis was confirmed in all cases by the demonstration of roentgenographic evidence of pneumonia and by the isolation and typing of a pneumococcus from the sputum. A variety of antibiotic agents were used — usually alone and rarely in combinations —


*From the Department of Medicine, Johns Hopkins Hospital and Johns Hopkins University School of Medicine.

†Formerly, fellow of the American Cancer Society.

and included penicillin, chlortetracycline and chloramphenicol. These agents in the dosage employed have been shown to be equally effective,[3-6] and it is considered valid therefore to consider this group as a whole.

The prognostic factors evaluated were age, extent of lung involvement, pneumococcal bacteremia, white-cell count, day of disease at onset of antibiotic therapy, pneumococcus type, chronic alcoholism and concomitant disease. Concomitant disease included chronic chest disease (asthma, chronic bronchitis, bronchiectasis and emphysema), arteriosclerotic coronary-artery disease, heart failure, diabetes mellitus, thyrotoxicosis, hemiplegia, cirrhosis of the liver, uremia, leukemia and lymphosarcoma. Cases were excluded when the concomitant disease could not be differentiated from the pneumonia.

The criteria utilized for evaluating the response of the patient to the antibiotic therapy were mortality and the frequency of abscess, empyema, atelectasis, roentgenographic or physical evidence of lung parenchymal involvement after thirty days of treatment and

TABLE 2. *Mortality Associated with Certain Clinical Findings in Reported Cases of Antibiotic-Treated Pneumococcal Pneumonia.*

| AUTHOR | ANTIBIOTIC | FACTOR | NO. OF CASES | MORTALITY |
|---|---|---|---|---|
| | | | | % |
| Dowling & Lepper[1] | Penicillin, chlortetracycline & oxytetracycline | Patient 10-19 yr. of age | 64 | 2.0 |
| | | Patient 20-29 yr. of age | 102 | 1.0 |
| | | Patient 30-39 yr. of age | 251 | 3.0 |
| | | Patient 40-49 yr. of age | 207 | 3.0 |
| | | Patient 50-59 yr. of age | 107 | 8.0 |
| | | Patient 60-69 yr. of age | 72 | 15.0 |
| | | Patient 70 & over | 57 | 15.0 |
| | | No bacteremia | 972 | 4.0 |
| | | Bacteremia | 96 | 13.0 |
| Dowling et al.[9] | Penicillin | No concomitant disease | 549 | 2.0 |
| | | Concomitant disease | 137 | 20.0 |
| Zubrod et al.[2-6] | Penicillin, chlortetracycline & chloramphenicol | Unilobar disease | 299 | 0.3 |
| | | Multilobar disease | 101 | 8.0 |
| Finland et al.[7,8] | Oxytetracycline & chlortetracycline | White-cell count under 10,000 | 15 | 33.0 |
| | | White-cell count over 10,000 | 86 | 6.0 |

continuation of a rectal temperature higher than 100°F. after ten days of treatment. The first four criteria are established ones. The last two were adopted as indicators of abnormally slow response. Such a response in the total group of patients (Tables 3 and 4) was rare enough to indicate that it is unusual and yet frequent enough for useful statistical analysis in a series of this size.

## RESULTS

The results are summarized in Table 5.

### Age

The disease was relatively benign in patients between the ages of ten and twenty-nine, with only a 1 per cent mortality and rapid recovery. In older patients mortality and evidence of a prolonged and complicated course increased progressively with increase in age.

### Extent of Lung Involvement

Unilobar disease was characterized by a 1 per cent mortality and a low prevalence of prolonged fever, slow resolution and complications. Multilobar disease was associated with a 10 per cent mortality and a relatively high frequency of prolonged fever, slow resolution and complications.

TABLE 3. *Duration of Rectal Temperature over 100°F. in 358 Patients with Antibiotic-Treated Pneumococcal Pneumonia.*

| DURATION OF FEVER | NO. OF CASES |
|---|---|
| *days* | |
| 0-5 | 253(71%) |
| 6-10 | 63(18%) |
| 11-15 | 21( 6%) |
| 16-20 | 5( 1%) |
| More than 20 | 16( 5%) |

### Pneumococcal Bacteremia

Cases without bacteremia were associated with 1 per cent mortality and a low prevalence of prolonged fever, slow resolution and complications. Cases with bacteremia were associated with a 9 per cent mortality and a relatively high frequency of prolonged fever, slow resolution and complications.

### White-Cell Count

The worst single prognostic sign evaluated was a white-cell count below 5000 before treatment. In such cases the mortality was 33 per cent. In survivors abscess occurred in 8 per cent, empyema in 17 per cent, fever lasting over ten days in 33 per cent and pulmonary involvement lasting longer than thirty days in 56 per cent. Higher white-cell counts carried a more benign prognosis.

TABLE 4. *Duration of Evidence of Lung Parenchymal Involvement in 358 Patients with Antibiotic-Treated Pneumococcal Pneumonia.*

| DURATION OF INVOLVEMENT | NO. OF CASES |
|---|---|
| *days* | |
| 0-5 | 16( 4%) |
| 6-10 | 168(47%) |
| 11-15 | 65(18%) |
| 16-20 | 31( 8%) |
| 21-25 | 11( 3%) |
| 26-30 | 7( 2%) |
| More than 30 | 60(17%) |

### Type of Pneumococcus

The mortality among patients with Type 1 and 3 infections was higher (6 per cent and 8 per cent re-

spectively) than that among those with infections due to other types. More cases of empyema were noted with Type 2 and 3 infections. No significant difference in the frequency of prolonged fever or slow resolution was observed with different pneumococcus types.

**Chronic Alcoholism**

Patients with chronic alcoholism had a slightly higher mortality (4 per cent) than those without alcoholism (3 per cent). However, this difference is not significant in a group of cases of this size. On the other hand, prolonged fever, slow resolution and

TABLE 5. *Prognostic Significance of Certain Clinical Findings in 358 Cases of Antibiotic-Treated Pneumococcal Pneumonia.*

| FACTOR | NO. OF PATIENTS | MORTALITY | PATIENTS WITH FEVER FOR MORE THAN 10 DAYS | PATIENTS WITH CONSOLIDATION FOR MORE THAN 30 DAYS | PATIENTS WITH ABSCESS | PATIENTS WITH EMPYEMA | PATIENTS WITH ATELECTASIS |
|---|---|---|---|---|---|---|---|
| | | % | % | % | % | % | % |
| Patient 10-29 yr. of age | 91 | 1.0 | 3 | 4 | 0 | 0 | 1.0 |
| Patient 30-49 yr. of age | 176 | 2.0 | 17 | 18 | 1.0 | 2.0 | 3.0 |
| Patient 50 & over | 91 | 8.0 | 16 | 27 | 1.0 | 1.0 | 4.0 |
| Unilobar disease | 269 | 1.0 | 7 | 9 | 0.4 | 1.0 | 2.0 |
| Multilobar disease | 89 | 10.0 | 27 | 44 | 3.0 | 6.0 | 8.0 |
| No bacteremia | 289 | 1.0 | 8 | 14 | 0.3 | 0.3 | 3.0 |
| Bacteremia | 69 | 9.0 | 29 | 34 | 4.0 | 9.0 | 4.0 |
| White-cell count less than 5000 | 12 | 33.0 | 33 | 56 | 8.0 | 17.0 | 0 |
| White-cell count 5000-10,000 | 47 | 0.0 | 23 | 26 | 2.0 | 2.0 | 4.0 |
| White-cell count more than 10,000 | 299 | 3.0 | 9 | 15 | 0.7 | 1.0 | 4.0 |
| Type 1 pneumococcus | 50 | 6.0 | 28 | 16 | 0 | 0 | 2.0 |
| Type 2 pneumococcus | 16 | 0.0 | 19 | 19 | 0 | 6.0 | 0 |
| Type 3 pneumococcus | 24 | 8.0 | 17 | 12 | 0 | 12.0 | 4.0 |
| Group 4 pneumococcus | 268 | 2.0 | 10 | 16 | 1.5 | 1.0 | 4.0 |
| No history of alcoholism | 257 | 3.0 | 5 | 10 | 1.0 | 0.5 | 3.0 |
| History of chronic alcoholism | 101 | 4.0 | 28 | 35 | 2.0 | 6.0 | 6.0 |
| No concomitant disease | 287 | 0.3 | 12 | 8 | 1.0 | 2.0 | 4.0 |
| Concomitant disease | 71 | 11.0 | 8 | 13 | 1.0 | 0 | 1.0 |
| Therapy begun on 1st day of disease | 142 | 5.0 | 7 | 9 | 1.5 | 1.5 | 0.7 |
| Therapy begun on 2d or 3d day of disease | 122 | 2.0 | 15 | 20 | 1.5 | 2.5 | 7.0 |
| Therapy begun on 4th day of disease or later | 94 | 2.0 | 13 | 24 | 0 | 2.0 | 4.0 |
| Averages | | 3.5 | 12 | 17 | 1.0 | 2.0 | 3.0 |

TABLE 6. *Analysis of Fatal Cases.*

| CASE NO. | AGE | LOBES INVOLVED | WHITE-CELL COUNT $x10^3$ | BACTEREMIA | PNEUMOCOCCUS TYPE | CONCOMITANT DISEASE |
|---|---|---|---|---|---|---|
| | yr. | | | | | |
| 1 | 53 | Right upper, middle & lower | 23.0 | Yes | 3 | Rheumatic heart disease: mitral stenosis & insufficiency; heart failure. |
| 2 | 49 | Left upper & lower & right lower | 0.75 | No | 20 | Myeloid leukemia; postirradiation leukopenia. |
| 3 | 56 | Left & right lower | 13.9 | Yes | 22 | Syphilitic aortic insufficiency; heart failure. |
| 4 | 27 | Right upper & middle | 4.68 | Yes | 19 | Hyperthyroidism; atrial fibrillation; heart failure. |
| 5 | 36 | Right upper & middle | 1.25 | Yes | 1 | None |
| 6 | 61 | Right lower | 13.45 | Yes | 1 | Emphysema |
| 7 | 49 | Left upper & right middle & lower | 2.55 | Yes | 1 | Healed bronchopleural fistula; fibrosis, left lower lobe. |
| 8 | 76 | Right & left lower | 18.0 | No | 19 | Coronary-artery disease with healed myocardial infarct & heart failure |
| 9 | 43 | Right upper & left lower | 11.7 | No | 3 | Coronary-artery disease & hypertension |
| 10 | 60 | Right middle & lower | 18.36 | No | 6 | Hypertension; uremia; thrombosis, right iliac artery; heart failure. |
| 11 | 81 | Right lower | 17.6 | No | 7 | Arteriosclerotic cardiovascular disease; senile dementia. |

empyema were significantly more frequent in chronic alcoholism.

#### Concomitant Disease

The presence of concomitant disease was associated with a relatively high mortality of 11 per cent, but with no increase in prolonged fever, slow resolution or complications.

#### Day of Disease at Onset of Therapy

This did not correlate significantly with mortality or the frequency of prolonged fever or complications. Patients treated on the first day of disease did show a significantly lower prevalence of slow resolution.

#### Analysis of Individual Deaths

This information is summarized in Table 6, which shows that multiple unfavorable prognostic signs were often present in the fatal cases. The deaths tended to fall into three groups. The first consisted of patients who were severely ill with extensive pneumonia and who died rapidly in shock, usually within twenty-four hours (Cases 5, 6, 7 and 9). The second group comprised patients who were severely ill with pneumonia and with some concomitant disease, and who died rapidly as the result of the disastrous interplay of their two diseases (Cases 1, 4, 8 and 10). In the third group, which was made up of those severely ill with pneumonia and some concomitant disease, the patients died less rapidly and apparently mainly from the effects of the concomitant disease (Cases 2, 3 and 11).

TABLE 6 *(Concluded).*

| CASE NO. | HISTORY OF CHRONIC ALCOHOLISM | DAY OF DISEASE ON WHICH THERAPY BEGAN | ANTIBIOTIC | INTERVAL FROM ONSET OF THERAPY TO DEATH | COMPLICATIONS | MODE OF DEATH |
|---|---|---|---|---|---|---|
| 1 | No | 1 | Penicillin | 17 hr. | None | Shock; pulmonary edema. |
| 2 | No | 1 | Penicillin | 7 days | None | Slow decline |
| 3 | Yes | 1 | Penicillin | 35 days | Meningitis; endocarditis. | Congestive heart failure |
| 4 | No | 1 | Penicillin | 3 hr. | None | Shock |
| 5 | Yes | 4 | Penicillin | 26 hr. | None | Shock |
| 6 | Yes | 1 | Penicillin | 9 hr. | None | Shock |
| 7 | Yes | 2 | Penicillin | 11 hr. | None | Shock |
| 8 | No | 1 | Chlortetracycline | 2 days | None | Congestive heart failure |
| 9 | No | 2 | Penicillin | 13 hr. | None | Shock |
| 10 | No | 1 | Chloramphenicol | 28 hr. | None | Shock; congestive heart failure. |
| 11 | No | 3 | Penicillin | 9 days | None | Sudden death after pneumonia had cleared considerably |

## Discussion

The evidence presented indicates clearly that, in antibiotic-treated pneumococcal pneumonia, increasing age, concomitant disease, multilobar involvement, pneumococcal bacteremia, leukopenia and infections due to Type 1 and 3 pneumococcus are associated with increased mortality. It is also apparent that in nonfatal cases with increasing age, chronic alcoholism, multilobar involvement, pneumococcal bacteremia, leukopenia or infections due to Types 2 and 3 pneumococcus, recovery is slower and suppurative complications more frequent. Individual analysis of the fatal cases of antibiotic-treated pneumococcal pneumonia reveals that more than one of these unfavorable prognostic signs existed in most of the patients who died. It is well known that these signs are associated with an unfavorable course in nonspecifically treated pneumococcal pneumonia (Table 1). It therefore appears that, although currently available effective antibiotic therapy greatly improves the outlook in pneumococcal pneumonia, it does not eliminate the prognostic significance of these signs. Regardless of therapy, when these signs are present, one must expect an increased mortality and an increased frequency of suppurative complications and slow resolution.

### Summary

In 358 cases of antibiotic-treated pneumococcal pneumonia, increasing age, concomitant disease, multilobar involvement, pneumococcal bacteremia, leukopenia and infections due to Types 1 and 3 pneumococcus were associated with an increased mortality. In nonfatal cases with increasing age, chronic alcoholism, multilobar involvement, pneumococcal bacteremia, leukopenia or infections due to Types 1 and 2 pneumococcus, recovery was slow and suppurative complications more frequent.


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# MEDICAL PROGRESS

## RADIOLOGIC EXAMINATION OF THE GASTROINTESTINAL TRACT


JOHN E. GARY, M.D.,* AND RICHARD SCHATZKI, M.D.†

BOSTON


ADVANCES in the radiologic examination of the gastrointestinal tract have not been touched on in this section for more than ten years. With few exceptions, only the more recent papers on various topics are reviewed here, with emphasis on subjects in which interest is most active.

### The Esophagus

#### Congenital Duplication

Frank and Paul[1] reported the first case of duplication diagnosed before death. A swallow of barium was seen to enter one large and one small canal in the lower two thirds of the esophagus. The two canals united just above the diaphragm. The patient was ten years old, and on observation again seven years later, the disproportion in the size of the two canals had increased. Dysphagia and regurgitation, the initial symptoms, had become less severe in the seven-year interval between the examinations.

In a study of 68 cases of duplication of the alimentary tract seen at the Children's Hospital in Boston, Gross, Holcomb and Farber[2] found 13 of the esophagus. In only 1 could a communication with the lumen be demonstrated. The others showed only a soft-tissue mass in the thorax that either displaced the esophagus or looked like an intramural, extramucosal tumor. In contrast, each of 3 duplications arising from a point in the gastrointestinal tract below the diaphragm, but presenting as a mass in the thorax, communicated with the lumen of the intestine, and all showed air-filled sacs. Of their total series, 51 per cent were in infants under five months, and only 8 were patients over two years old. In 40 per cent of the total series the duplication arose from the ileum, and only 1 of these showed a communication with the lumen. A varying degree of obstruction was the chief finding in most cases.

#### Varices and Portacaval Shunt

Blakemore[3] comments on the prognostic significance of the effect of portacaval shunt on varices as seen radiologically. Of 75 cases examined before and after operation varices disappeared in 26, and in none of these was there postoperative hematemesis. Among 34 cases that showed a decrease in the size of the varices after operation there were 2 cases of postoperative hematemesis. Fifteen cases showed no x-ray change, and 9 of these had postoperative hematemesis. There was good correlation between the disappearance of varices and the drop in the pressure in the portal vein (as measured during the operation) after the shunt was completed.

#### Lower End of the Esophagus

*Esophagogastric junction (hiatus hernia).* Much interest has centered in recent years on the lower end of the esophagus, particularly on the junction of the esophagus and stomach. This is largely due to progress in thoracic surgery, which has made surgery here as safe as on the abdominal portions of the gastrointestinal tract.

Careful studies have shown that some apparently well established concepts are inconclusive or even wrong.

The difficulty begins in the attempt to locate the


*Assistant in radiology, Harvard Medical School; associate radiologist, Mount Auburn Hospital, Cambridge, Massachusetts.

†Instructor in radiology, Harvard Medical School; radiologist-in-chief, Mount Auburn Hospital, Cambridge, Massachusetts.

exact junction of the esophagus and stomach, a decision that is of obvious importance in the diagnosis of hiatal hernias of the stomach. Lerche[4] made a careful study of this area in 80 cadavers. His monograph demonstrates in particular the muscular pattern of the lower esophagus and the gastrocardiac junction. This is of great interest and should be read in the original. The conclusions that Lerche draws from his studies on the physiology of the lower end of the esophagus and the cardia, as well as the relation of these structures to the diaphragm in vivo, are open to question.

The determination of the esophagogastric junction in normal persons at times is easy. The stomach has a characteristic shape, which is quite different from that of the tubular esophagus. It lies below the diaphragm, and its mucosal pattern is different from that of the esophagus. Finally, there is a definite physiologic closing mechanism at the junction of the two, mainly represented by the diaphragm (right crus), the sharply angled junction of the two organs and also by a sphincter in the lowermost end of the esophagus, which, although anatomically often disputed or rejected, can be demonstrated roentgenologically.[5-7] If all these criteria are present in a given case, the localization is easy. When a small portion of the stomach herniates into the chest identification of the esophagogastric junction becomes considerably more difficult for the roentgenologist, the endoscopist, the surgeon and even the anatomist.

The knowledge that may be gained by anatomic studies of this area is limited, owing to the marked contractibility of the esophagus in its longitudinal direction, which may change its relation to the diaphragm. Roentgenologic and endoscopic examination in conjunction with surgery may give information when anatomy fails but is often far from decisive. Allison and Johnstone, in several papers, have most clearly discussed the problems of this particular area. In a study of early gastric herniation through the esophageal hiatus, Johnstone[6] emphasizes the difficulties in the diagnosis of this condition. A small pouch immediately above the diaphragm may represent ballooned esophagus or a small segment of herniated stomach. The folds in the pouch at times are unmistakably gastric folds. Frequently, however, the identification of the type of mucosa is impossible. Stretched gastric mucosa may look like esophageal mucosa, and bunched-up esophageal folds may simulate tortuous gastric folds. Finally, marked mobility of the mucosa of the gastroesophageal junction upon the underlying muscularis increases the difficulty in proper identification of a supradiaphragmatic gastric pouch. Roentgenologic studies after the mucosal junction has been identified with dural clips[6,8] have proved to be of great interest. They have also shown that the esophagus normally ends either at or just above the esophageal hiatus and that the so-called intra-abdominal portion of the esophagus is actually a portion of the stomach that at times is poorly unfolded.

Probably the most reliable roentgenologic sign in the diagnosis of hiatus hernia is the demonstration of a sphincter at the upper end of a questionable pouch. The main sphincter mechanism — that is, the diaphragm — is obviously not functioning at this level, but a constriction of the lowermost portion of the esophagus, functioning as a sphincter, can often be clearly identified, although it is usually much less efficient than the complete, normal sphincter mechanism. At times, this narrowing above the herniated stomach maintains the characteristic bayonet-like shape that it normally has when it lies at the hiatus of the diaphragm.[5] Even with all these studies, differentiation of a small hernia from a ballooned esophagus may be impossible. Johnstone believes that the demonstration of regurgitation into the esophagus is actually the most important clinical feature; it may occur without herniation but is more frequent in the presence of a hernia. He thinks that little clinical attention need be paid to any small supradiaphragmatic pouch unless regurgitation is present.[6,9] Evans[10] stresses the difficulties in the diagnosis of the small hernia, and also emphasizes the importance of demonstrable regurgitation.

### Esophagitis and Esophageal Ulcer

A large number of papers are concerned with the roentgenologic appearance and the etiology of esophagitis and esophageal ulceration. Esophagitis with ulceration and fibrosis may occur without herniation of the stomach (Winkelstein et al.[11]). In this group fall cases of esophagitis that follow prolonged gastric intubation. More frequently, however, severe esophagitis is associated with hiatus hernia. The combination of hiatus hernia and esophagitis, with or without esophageal ulceration and fibrosis and occasionally combined with duodenal ulcer, is an entity that has interested many authors in the past.[12]

The interesting and clinically important question of whether the hiatus hernia precedes the esophagitis and ulceration or whether longitudinal contraction of the esophagus secondary to esophagitis produces the herniation has not been answered unequivocally. The opinion of authors in recent years tends to stress reflux of gastric juice into the esophagus owing to an incomplete closing mechanism at the esophagogastric junction as the primary mechanism.[9,13-15] Since, according to these authors, reflux is more common in patients with herniation of the stomach, a hiatus hernia is a predisposing factor for esophagitis, which may then result in superficial ulceration and fibrosis, with narrowing of the involved esophageal segment. "Reflux esophagitis" has become a well established entity. This emphasis on regurgitation provides a good working hypothesis, and no better one has been proposed. Many patients with regurgitation, however, have no symptoms and no evidence of esoph-

agitis, and, contrariwise, regurgitation frequently cannot be demonstrated in patients with esophagitis. Further study by radiologists, endoscopists, surgeons, pathologists and anatomists is still necessary.

Occasionally, characteristic peptic ulcers are found at the esophagogastric junction of herniated stomachs in patients with no clinical or roentgenologic evidence of esophagitis and with only a slight degree of mucosal inflammation near the ulcer on endoscopic study. Pain and bleeding, rather than dysphagia, are the most common clinical complaints although stenosis may occur. Whereas the ulceration in reflux esophagitis is usually superficial, extending frequently around the circumference of the esophagus, the above ulcers are inclined to grow in the longitudinal, rather than in the circumferential direction of the esophagus. They behave like peptic ulcers of the stomach in that they may cause massive hemorrhage and may perforate into surrounding structures. According to Barrett[16] these ulcers arise in gastric mucosa at the junction of the herniated stomach with the esophagus or in gastric mucosa of the lower esophagus. They are actually gastric ulcers. The roentgenographic demonstration of gastric mucosa in the esophagus is not possible. A combination of reflux esophagitis with peptic gastric ulcer of the esophagus may occur in such cases.[17]

#### Anomalies of the Esophagogastric Junction in Infancy

The behavior of the esophagogastric junction in babies has interested a number of authors in recent years. Neuhauser and Berenberg[18] described persistent vomiting in infants, usually in the neonatal period, caused by insufficiency of the normal hiatal closing mechanism ("chalasia"). This reflux, characteristically seen in horizontal fluoroscopy, is easily cured if the infant is kept in the upright position during the feeding and for half an hour afterward. Neuhauser and Berenberg postulate a transient neuromuscular abnormality as the cause of the phenomenon.

Other authors, especially in England, stress another mechanism of insufficiency of the cardiac sphincter. They report a high frequency of small hiatal hernias in infants leading to regurgitation. As in adults, this may cause esophagitis and eventually stricture. The majority of the infants improve on a conservative regimen, strictures occurring in about 10 per cent of the cases. In England a congenital anomaly of the hiatus is at present the favored explanation of this abnormality. The concept is interesting, but the rarity of herniation in young adults makes it difficult to accept the high frequency of hiatal hernia in infants as described by some of these authors. Astley and Carré[15] emphasize the fact that the herniated portion of the stomach may be small and may look like either a pouch or a tubular structure. If the herniated stomach is tubular in shape, the cardia may be scarcely visible roentgenologically. The diagnosis of hernia in these cases is made exclusively by the appearance of the mucosal folds.

The proof of herniation in some of the publications is at times based entirely on the appearance of the mucosal pattern, a difficult and frequently not a reliable differential diagnostic criterion.

Wolf, Som and Marshak[14] regard some of the anomalies in the lower end of the esophagus found in adults as being due to congenitally poor fixation of the lower end of the esophagus.

#### Lower Esophageal Ring

During the past year Ingelfinger and Kramer[19] and Schatzki and Gary[20] described patients with dysphagia that did not fit into any of the commonly discussed groups. Intermittent episodes of dysphagia characterized the clinical picture. Roentgenologically, a smooth, thin, concentric diaphragmlike narrowing was seen in the lower esophagus, approximately 5 cm. above the diaphragm. The maximal diameter of the ring appeared to be fixed in a given patient.

The roentgenologic appearance simulated a small area of fibrosis, but several features were different from fibrosis. The 11 patients described by these authors were males, but the syndrome, as could have been expected, is not limited to males. Schatzki and Gary[21] have now seen a total of 17 of these patients, 8 males and 9 females.

Esophagoscopy gave no evidence of esophagitis or ulcer in any of the cases and, with the exception of extreme cases, did not demonstrate the ring itself. Ingelfinger and Kramer[19] believe that the ring is not necessarily preformed, but may represent a contraction in the esophagus itself. Schatzki and Gary are inclined to believe that the ring represents the herniated esophagogastric junction. They regard the narrowing as caused not by an abnormal muscular contraction but by an inability of the esophagogastric junction to distend beyond a certain diameter. The nature of the abnormality and its origin are not known, but the clinical and roentgenologic pictures are characteristic.

A similar roentgenologic appearance has occasionally been described as an incidental finding in patients *without* dysphagia. Schatzki and Gary[21] find such asymptomatic rings frequently (probably in 1 or 2 per cent of adults). They believe that the question of whether or not the ring leads to dysphagia depends mainly on its maximal diameter and to a lesser degree on the eating habits of the patient.

### Stomach

#### Methods of Examination

Careful fluoroscopic observation and spot films remain the cornerstone in examination of the stomach, but additional maneuvers, some old and some new, have been described in recent years. Distention of the stomach with 500 to 1500 cc. of air by means

of a gastric tube after a single swallow of barium is reported to help differentiate large normal mucosal folds from polyps and malignant tumors. The former are obliterated by pressure whereas the latter remain unchanged when the stomach is inflated.[22]

A tube with a balloon near its tip and an opening beyond the balloon can be used to advantage to demonstrate the afferent loop after gastrectomy. If the tube passes into the efferent loop the balloon is inflated to occlude the lumen. Barium taken by mouth then passes from the gastric stump into the afferent loop only, and the anastomotic area is well filled. If the tube enters the afferent limb the balloon is inflated, and barium injected through the tube to fill the afferent limb beyond the balloon. Stump ulcers have been demonstrated by this technic.[23] We have had no experience with the method.

The cause of shortening of the lesser curvature seen occasionally in benign ulcer was investigated by Hinds and Harper.[24] They found this complication to be due to inflammation and fibrous thickening of the lesser omentum. Consequent shortening of this ligament pulls up the antrum, and a pouch is formed by the dependent portion of the stomach, resulting in delay in gastric emptying.

#### Mass Surveys for Carcinoma

Every year 40,000 people in the United States and Canada die from cancer of the stomach.[25] Curability in patients who reach the hospital is at present about 5 to 7 per cent. What can be done to increase the curability? Earlier diagnosis appears to be the obvious answer. Despite the development of other methods, such as gastroscopy and abrasive exfoliative cytology, roentgenologic examination remains the only practical method available for detection of cancer of the stomach.

If every patient with symptoms of cancer of the stomach were examined immediately, if the correct diagnosis were made and if the patient were operated on, the death rate would drop. A still more dramatic improvement would result if cancer could be discovered before it caused symptoms.

Mass surveys of people without gastric symptoms seem to be a logical approach. Is such a survey feasible, and what might the results be?

In 1944 St. John, Swenson and Harvey[26] reported on survey examinations performed on 2413 persons fifty years of age or older. The usual careful complete fluoroscopic and radiographic examination of the stomach was not done; intentionally, only a rapid fluoroscopic survey was attempted on these patients, who had no significant digestive symptoms. Two carcinomas and 1 lymphosarcoma were detected. One of the patients was well after nine years, 1 died after six years (cause unknown), and the third died shortly after operation. Using similar methods, Sherman[27] found 2 malignant lesions in 2858 asymptomatic persons forty-five years or older. In an additional 2000 fluoroscopic studies, however, Sherman found no cancers. Dailey and Miller,[28] on fluoroscopic examination of 500 patients forty-five years or over found 1 polyp but no cancers.

In contrast to these purely fluoroscopic survey examinations, other authors have tried a purely radiographic approach, with a photofluorographic system similar to that used for mass surveys of the chest. Such examinations became feasible with the introduction of faster photographic equipment, such as the Schmidt camera and, more recently, the Odelca camera. Roach, Sloan and Morgan[29] reported on 10,000 examinations performed at Johns Hopkins Hospital with such a system; 27 proved tumors were found in the stomach in this series. However, only 1 patient had no symptoms, and 4 minimal symptoms; the rest showed moderate to severe symptoms. Of these 27 cases the tumor had gone beyond the confines of the stomach in 23. Obviously, patients with symptoms were not excluded from the survey, and not many early cases were discovered. It is interesting that an additional 27 suspected tumors were found in which operation could not be done because the patient was unwilling to be operated on.

Another report on photofluorographic mass-survey studies comes from Jefferson Hospital in Philadelphia, where Wigh and Swenson[30] used photographic equipment in 1947 before the Schmidt camera was available and continued it later in combination with the Schmidt camera; 5096 patients forty years or older were examined. They had no gastrointestinal symptoms sufficient to attract the physician's attention. Three cancers were found; 2 patients had no demonstrable metastases at the time of operation, but the third did have and died shortly afterward from peritonitis. Eight polyps were diagnosed, 5 of which were excised. Both the Hopkins and Philadelphia groups emphasize the point that this method is used only as a screening device to be followed by conventional fluoroscopic and radiographic study when suspicion arises from the screening test. In the cases surveyed by Wigh and Swenson, for instance, 322 were recommended for routine examinations.

In contrast to these short-cut methods, another approach has been described by Rigler.[31] He employed the conventional complete roentgenologic method of examination but used, in addition to age, selective factors that were expected to result in a higher yield. Such a factor was pernicious anemia. Of 248 patients with pernicious anemia, 6 per cent had cancer, and 7 per cent benign polyps. Another factor was the low gastric acidity in patients with cancer of the stomach; 544 people over fifty years of age with less than 30 units of free hydrochloric acid were examined. Three cancers and 19 polyps were found. The high yield in these groups is quite striking.

The Johns Hopkins group concluded, with some

resignation, that the survey examination was not too helpful in the detection of unsuspected, asymptomatic cancer of the stomach. On the other hand, Wigh and Swenson considered it feasible, practical and financially possible.

Opponents of the mass-survey examinations of the stomach[25,32] point out that the symptomless period of gastric cancer may be short and that therefore frequent re-examinations are necessary. Since the photofluorographic examination of the stomach takes considerably more time than miniature chest roentgenography, it is doubtful whether a thorough screening of the population could be done. In addition the large number of examinations by conventional methods made necessary by the mass survey for doubtful cases may be prohibitive.

The moment for general mass surveys has not yet arrived, but it is fortunate that such surveys are being made in certain centers. Their further results will be watched with great interest.

#### Superficial Spreading Carcinoma

Golden and Stout[33] described this special type of gastric cancer, which accounted for 14 per cent of 200 cases studied by them. It is characterized radiologically by minimal ulceration and a large surrounding area in which peristalsis is absent. Pathologically, these lesions spread through the mucosa and submucosa, and spare the muscular coat of the stomach.

#### Varices

Evans and Delany[34] were able to demonstrate definite x-ray evidence of gastric varices in 16 out of 40 patients who had portal hypertension and esophageal varices. Varices in the stomach appear as hemispherical mucosal elevations in the fundus or as a lobulated contour defect around the cardia. Portal venograms show them very clearly.

#### Amyloidosis

Cooley[35] described a case of primary amyloidosis with stomach involvement. Nodules were seen in the wall of the stomach that were difficult to differentiate from cancer. He believed that the wall was more pliable than that in cancer. Shipps and Brannan[36] presented another case in which the mucosal folds were very thick but were effaced by peristalsis.

#### Tuberculosis

Ostrum and Serber[37] reported 2 cases of tuberculosis in the stomach and 1 in the duodenum. From these, and a review of other cases, they concluded that tuberculosis should be thought of if an infiltrating lesion or ulcer involved both the stomach and duodenum, especially if fistulous tracts could be seen originating from the involved part of the stomach. Tuberculous adenitis, which was a prominent feature, was often found peripherally long before the stomach was involved.

#### Emphysematous Gastritis

Five cases of this rare condition have been reported, and only the patient described by Welch and Jones[38] survived. The diagnosis can be made from the plain film of the abdomen. The gastric air shadow is silhouetted by a halo of innumerable small gas bubbles, which lie within the wall of the stomach. Infection of the stomach wall by a gas-forming organism causes the striking x-ray changes. Weens[39] reported the first case diagnosed by x-ray study, and Henry[40] presented the only case so far described in an infant.

#### Volvulus

Although volvulus may be chronic, the usual case presents a history of intermittent attacks of acute, colicky pain in the upper abdomen.[41] An abnormally high left leaf of the diaphragm is frequently seen. The greater curvature lies above the lesser curvature when the stomach twists on its longitudinal axis, with the duodenum and cardia as fixed points. A definite spiral twist of the mucosa should be identified when barium is given. Treatment is usually surgical, with reduction and fixation of the abnormally mobile stomach.

#### Rupture of Spleen

A dilated stomach, with a ragged, serrated appearance of the greater curvature, was seen in 7 of 15 cases of rupture of the spleen due to trauma.[42] Four showed obliteration of the splenic shadow, and 2 had compression of the fundus of the stomach laterally. The last is of importance only if repeated films show that the degree of compression increases, since some compression may occur normally. Decreased excursion of the left leaf of the diaphragm may also be present. It is important to remember that there may be no x-ray abnormalities in this condition.

#### Villous Adenoma

This variety of mucosal tumor should always be resected since microscopical examination usually shows malignant areas. Walk[43] presented 2 cases that demonstrated large antral masses with a very irregular "soap-bubble" surface, and this surface appearance is described as characteristic of the tumor.

#### Prolapse of Gastric Mucosa into the Duodenum

Prolapse of gastric mucosa into the duodenum was first reported by Schmieden in 1911 in a case in which it was found accidentally during an operation. Eliason and Pendergrass described the roentgenologic appearance in 1926, but not until the last decade, particularly after a paper by Scott[44] in 1946, has this prolapse, its roentgenologic appearance and the question of its clinical significance received widespread attention and discussion. The prolapse is an unusually rare finding at autopsy. Of the many roentgenologic cases reported in the recent literature only a few have been verified at operation. The

clinical symptomatology is variable. The diagnosis is based exclusively on radiologic findings, and a critical review of these findings appears indicated.

The description of the roentgenologic appearance of what is thought to be prolapse varies little from author to author. A smooth or lobulated filling defect in the base of the duodenal cap is considered to be the classic picture of prolapse. This defect may be symmetrical or more pronounced on the upper or lower side of the cap. The resulting configuration has been variously compared to an umbrella, a cauliflower, a mushroom and an atomic bomb. In less pronounced cases, a single fold may produce a small linear defect through the pylorus into the cap.

The various authors, however, while describing roentgenologic features of the prolapse, do not agree on the frequency of its occurrence. Scott[44] reports the frequency of prolapsed mucosa as 1 per cent of all patients examined roentgenologically, New[45] as 2.9 per cent, Melamed et al.[46] as 6.2 per cent, Feldman and Myers[47] as 14 per cent, Levin and Felson[48] as 18 per cent, and Bartels and Eltorm[49] as 18 per cent. The last two authors found no less than 50 per cent of prolapse in another small series of patients without gastric symptoms. This discrepancy is difficult to explain. Perhaps, the borderline between the appearance of the base of the duodenal cap in normal cases and that in mucosal prolapse is not so definite as was thought originally. A critical review of the illustrations in the literature forces one to believe that the proof of prolapse of the mucosa is frequently lacking and that the roentgenologic appearance may often have a different explanation. At times thick folds of the cap itself appear to be the cause of the defect; at others simple bulging of the pylorus into the base of the cap may be responsible. Quite frequently, an end-on view of the duodenal cap with incomplete central filling appears to be a better explanation of the roentgenologic picture. Finally, the so-called prolapsed mucosa can often be analyzed as antral mucosal folds projected on the shadow of the cap. A good review of various features that may produce a picture similar to mucosal prolapse may be found in an article by Schröder.[50]

The symptomatology as given by the various authors is quite variable, including most of the usual epigastric complaints, such as distention, heartburn, gaseous eructation, cramplike pain, belching and vomiting. Hypochromic anemia, tarry stools and occasional severe hemorrhage have been thought to be due to prolapsed mucosa. A few cases of pyloric obstruction have been reported. On the other hand some authors believe that the prolapse represents a normal physiologic variation and that it causes no symptoms. It is not surprising to find in this camp the authors who had the highest prevalence of mucosal prolapse in their patients.

Summarizing our own experience and that of others, we believe that there is operative proof in some cases reported in the literature that prolapse of the gastric mucosa may occur. We believe that, in spite of a constantly growing literature on the subject, the clinical significance of prolapse lacks sufficient proof, and we make the diagnosis rarely. At present, watchful caution appears to us the proper attitude to this problem.

*(To be concluded)*

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## MEDICAL INTELLIGENCE

# ACUTE HALLUCINOSIS SECONDARY TO PAGITANE HYDROCHLORIDE ADMINISTRATION

MICHAEL G. PIERIK, M.D.*

PROVIDENCE, RHODE ISLAND

VARIOUS compounds of the atropine group have been used with success in treatment of the several types of paralysis agitans. For satisfactory control of symptoms, doses approaching the toxic level are necessary. Most clinicians are familiar with the manifestations of mild overdosage. These include oral dryness, blurred vision, tachycardia and pyrexia. Less well known are the occurrence of delirium, confusion and even frank paranoid psychosis. Fortunately, in about 75 per cent of such cases, the minor symptoms listed above occur before mental changes and are valuable warning signs. Since most of the patients with paralysis agitans are in the arteriosclerotic early senile group, cerebral symptoms and urinary retention are most apt to be troublesome.

Pagitane Hydrochloride is a potent antispasmodic said to be of value in control of the tremor and rigidity in the several forms of paralysis agitans.† Chemically it is 1-phenyl, 1-cyclopentyl, 3-piperdino, 1-propanol hydrochloride. It has an action on muscle spasticity resembling that of atropine, with similar side effects, which include minor symptoms of oral dryness, dizziness, blurring of vision and transient nausea. More serious manifestations such as hallucinations and disorientation occur in higher doses. There is apparently a wide variation in individual tolerance.

The following case illustrates an acute episode of hallucinosis after one day of therapy:

M. L., a 53-year-old woman, was admitted to the Boston Dispensary Arthritic Clinic on April 8, 1954, for evaluation of pain in the left thigh and hip. This pain was referred to the anterior thigh muscles, aggravated by walking and cramplike in character.

The past history was negative for mental disease, alcoholism or hallucinations. No symptoms suggestive of encephalitis were admitted.

On examination the patient presented the typical tremor, masklike facies and rigidity of paralysis agitans. Examination of the musculoskeletal system was normal except for stiffness and spasm in the vastus musculature of the left leg on motion. In particular there was no limitation of motion or pain in the left hip joint proper.

X-ray films of both hips were normal.

A diagnosis of arteriosclerotic paralysis agitans was made. It was considered that the thigh pain was secondary to muscular spasm. Pagitane Hydrochloride in doses of 2.5 mg. 3 times daily, was advised. During the same evening the patient inadvertently took a total of 7.5 mg. in 1 dose. On the following day she had a delusion that there was a masked man sitting in her living room who was going to punch her. Her husband tried to convince her that the room was empty. She agreed that the situation was absurd but continued to be plagued by various "visions." On the next day 5 mg. of Pagitane was taken. That evening she insisted that someone was spying on her from the back yard. Despite voluntary reduction of the medication to 2.5 mg. daily, visual and auditory hallucinations continued for the next three days. On 1 occasion police were called to "catch the masked bandit in the cellar." There were attendant nightmares alternating with insomnia. The disturbances gradually decreased in frequency. When seen in the clinic 1 week later, she was rational and denied hallucinations or delusions.

During this period her husband noted that she was nearly completely free of "shakes" for the 1st time since the onset of the disease. She claimed that her thigh pain had almost disappeared. At the time of her visit to the clinic the tremor and rigidity were estimated to be about 50 per cent improved. Ambulation was much easier. The thigh pains were present but much less severe. She was able to do her housework on schedule for the 1st time in months.

### SUMMARY

Pagitane Hydrochloride gave satisfactory symptomatic relief in a case of arteriosclerotic paralysis agitans. However, a minimal overdose precipitated an acute hallucinating state. Symptoms persisted for four days despite reduction in dosage. Careful regulation of dosage of this drug appears necessary.

250 Elmwood Avenue

*Formerly, trainee in arthritis and metabolic diseases, National Institutes of Health, and fellow in internal medicine, New England Center Hospital, Boston.

†Magee, K. R., and DeJong, R. N. Antispasmodic Compound 08958 in treatment of paralysis agitans. *J.A.M.A.* **153**:715-718, 1953.

# DISSECTING AORTIC ANEURYSM DURING PREGNANCY*

CAPTAIN WILLIAM MANDEL, USAF (MC),†
CAPTAIN E. WARREN EVANS, USAF (MC),‡
AND CAPTAIN R. L. WALFORD, USAF (MC)§

IN 1944 Schnitker et al.[1] reported a case in which a dissecting aortic aneurysm developed on the twelfth post-partum day. They collected 23 cases of this complication in association with pregnancy. Since their article 12 similar cases have been recorded.[2-13] In the following case the sudden death during pregnancy was due to a dissecting aortic aneurysm.

## CASE REPORT

A 20-year-old woman was admitted to the hospital in the 3d month of her 1st pregnancy because of sudden onset of nausea, vomiting and headache of 1 day's duration. The headache was throbbing in type and similar, though more intense, to what she had been experiencing for several months. The headaches had been attributed to an otherwise asymptomatic hypertension that had been diagnosed 3 years previously.

At the age of 9 she had had scarlet fever, and "dropsy" had developed. After 4 months of bed rest she was said to have recovered completely. Three members of her family had hypertension.

Physical examination showed a well developed, slender woman who appeared chronically ill. She weighed 116 pounds and was 65 inches in height. The temperature, pulse and respirations were normal. The blood pressure was 220/140 in the right arm, and 210/130 in the left. There was marked bilateral pulsation of the carotid arteries. The left border of the heart was percussed beyond the left midclavicular line. The apical impulse was felt in the left 5th anterior intercostal space 2 cm. lateral to the midclavicular line. There were no thrills. The cardiac rhythm was normal. The aortic 2d sound was louder than the pulmonic. A Grade 1 soft systolic mitral murmur and a Grade 2 blowing systolic aortic murmur were heard. All pulsations in the peripheral arteries were present. Pelvic examination disclosed an enlarged uterus.

The specific gravity of the urine varied from 1.012 to 1.018, and there was a + to +++ test for protein. Occasional hyaline and granular casts and a few white and red blood cells were seen on microscopical examination of the sediment. The blood urea nitrogen was 15 mg. per 100 cc. Phenolsulfonphthalein excretion was 7 per cent in 15 and 35 per cent in 45 minutes. The blood Wassermann and Kahn tests were negative. The hemoglobin was 12 gm. per 100 cc., the red-cell count 4,300,000, and the white-cell count 9000. The differential count was normal. The sedimentation rate was 16 mm. per hour. The serum sodium was 138, the chloride 98 and the potassium 5 milliequiv. per liter. The total serum protein was 6.47 gm. per 100 cc. Fluoroscopic and roentgenographic examination of the heart showed that its transverse diameter was 20 per cent above the predicted normal diameter, the shadow of the left ventricle being prominent. An electrocardiogram was normal. An intravenous pyelogram revealed mild bilateral calyceal dilatation.

At rest the blood pressure ranged from 180/120 to 220/140. There was no change in blood pressure after the intravenous injection of 5 mg. of Regitine. The patient felt well on the 2d hospital day and remained so until discharge. The diagnoses were chronic glomerulonephritis, hypertensive cardiovascular disease and pregnancy.

She was well for 6 weeks, when nausea, vomiting and severe chest and back pain suddenly developed. She did not complain of weakness, dizziness, headache, shortness of breath or visual disturbance. When examined she was acutely ill and was turning from side to side to obtain relief from the pain. The bilateral pulsating carotid vessels were again noted. The blood pressure in the right arm was 248/142, and that in the left 230/80. The apical impulse was seen and felt in the 6th left intercostal space at the anterior axillary line. A systolic aortic thrill was felt. The cardiac rhythm was normal, and the rate was 120 per minute. A Grade 5 rough systolic aortic murmur and a Grade 4 blowing aortic diastolic murmur were heard. The pulsations in the femoral arteries were present. During the examination, and within 15 minutes of admission to the ward, the patient suddenly gasped and became cyanotic, her neck became rigid, her pulse disappeared, and she died.

At autopsy the pericardial sac contained 700 cc. of blood. The heart weighed 450 gm. The hypertrophied left ventricle measured 2 cm. in thickness. The coronary vessels showed mild atherosclerosis. The right coronary artery was 30 per cent occluded near its origin by an atherosclerotic plaque. The intimal surface of the aorta was generally smooth but disclosed an occasional yellow slightly elevated streak and irregular oval circinate atherosclerotic bands. There was a 1.5-cm. T-shaped posterior perforation of the intima and media of the aorta 2 cm. above the aortic cusps. This perforation led to a sac-like dilatation, containing 100 cc. of blood, that communicated with the pericardial sac. There was dissection of the aorta from the point of perforation to 4 cm. above the bifurcation of the abdominal aorta. At this point the dissection re-entered the aortic lumen through a 1-cm. horizontal slit. The intima and media had remained attached over the anterior 40 per cent of the aortic circumference. The dissection involved the origins of the renal arteries for 0.5 cm.

The kidneys together weighed 255 gm. and except for a dusky color were grossly normal. The uterus was 22 cm. in length and contained an intact fetus that measured 13 cm. from crown to rump.

On microscopical examination the dissection involved the outermost layers of the aortic media and showed a sharp advancing edge. There was striking focal degeneration of elastic fibers, particularly in the ascending aorta, that was associated with metachromatic material. This material gave a myxomatous appearance with the hematoxylin and eosin stain. In some of the involved areas the poorly supported vasa vasorum were dilated, and red blood cells had extravasated into the degenerated media. The intimal endothelium was preserved, but there was extensive subintimal fibrosis. Foamy lipid-filled cells were occasionally present in profuse numbers in these regions. These changes elevated the intimal endothelium, and at various sites the atherosclerotic material had burrowed deeply into the underlying fragmented media. The adventitia was involved by a proliferating fibrous process that was associated with perivenous lymphocytic infiltration. The adventitial vasa of the ascending aorta were sclerotic.

The kidneys were diffusely hyperemic. There was mild focal proliferation of interstitial tissue. The vessels showed lamellar intimal thickening, and the muscular coats of the small arteries were moderately hypertrophied. An occasional dilated tubule contained eosinophilic casts. There were no striking changes in the other organs.

## DISCUSSION

Of the 49 cases of dissecting aneurysm that occurred in women below forty years of age reviewed by Schnitker et al.,[1] 24 were in pregnancy. The principal features of the 12 cases of dissecting aneurysm occurring during pregnancy since then are outlined in Table 1. One of these patients was forty-three years old but is included for completeness. During the same period 9 cases were reported in nonpregnant women under forty years of age. Except for pregnancy there were no essential clinical or patho-

*From the Medical and Laboratory services, 3345th USAF Hospital, Chanute Air Force Base, Illinois.
†Formerly, instructor in medicine, University of Illinois College of Medicine.
‡Physician, Medical Service, 3345th USAF Hospital.
§Instructor in pathology, School of Medicine, University of California at Los Angeles.

logical differences between the two groups. Including the case reported above, there have been 70 recorded cases of dissecting aortic aneurysm in women under forty. Thirty-six of the patients (51 per cent) were pregnant. These figures may be weighted, for dissecting aortic aneurysms are more likely to be reported when they occur during pregnancy than when pregnancy is not present. However, it is probable that this represents a true increase.

Theories concerning the etiology and pathogenesis of dissecting aortic aneurysm in younger persons have recently been reviewed.[14-17] The case presented above illustrates several of these theories. The patient was pregnant (hormonal imbalance) and had hypertension. There was considerable degeneration of the elastic tissue of the aorta (medionecrosis). Proliferation of the vasa vasorum, with early rhexis and hemorrhage into degenerated media, was present. These elastica and vascular changes were most prominent in the outer third to two thirds of the media. There was considerable sclerosis of adventitial vasa in the ascending aorta. These five factors were probably interrelated and show the difficulty of establishing a single and primary cause for the dissection.

TABLE 1. *Cases of Dissecting Aneurysm during Pregnancy Reported since 1943.*

| Case No. | Author | Age | Gravidity | Parity | Month of Pregnancy | Clinical Data | Gross Autopsy Findings | Microscopical Findings |
|---|---|---|---|---|---|---|---|---|
| | | yr. | | | | | | |
| 1 | Billingshurst[2] (1943) | 23 | 1 | 0 | 9 | Past history noncontributory; onset of unconsciousness during labor; patient regained consciousness & delivered normal child; sudden death on following day. | Hemopericardium; 0.8-cm. longitudinal aortic intimal tear above aortic valve; coarctation of aorta. | * |
| 2 | Kinney et al.[3] (1945) | 23 | 1 | 0 | * | Past history noncontributory; sudden onset of pain in neck & left arm; continued pain for 5 days; blood pressure normal; Grade 2 systolic murmur; absent femoral pulsations; sudden death; cesarean section after death; child lived for 3 hr. | Hemopericardium (750 cc.); 3.5-cm. oblique intimal tear 1 cm. above aortic valve, with dissection of ascending aorta; coarctation of aorta & bicuspid aortic valve. | Intima normal; media showed loss of muscle & elastic fibers with mucoid degeneration proximal to coarctation; "scar" tissue near tear. |
| 3 | Palmer & Mathisen[4] (1946) | 29 | * | * | 5 | Past history of hypertension; nausea, vomiting & albuminuria on admission; fetus dead; no pain or murmurs; sudden death. | Hemorrhage into left thoracic cavity; intimal tear at junction of transverse & descending aorta; dissection to diaphragm; arteriosclerosis present; renal infarct. | "Medial necrosis & arteriosclerosis" as well as severe arteriolar nephrosclerosis |
| 4 | Johnson & Frank[5] (1947) | 34 | 3 | * | 8½ | Past history noncontributory; moderate lumbar pain; patient died suddenly; cesarean section after death; viable child. | Hemopericardium (500 cc.); v-shaped tear 1.2 x 1.5 cm. above right coronary ostium; dissection to common iliac vessels; "mild atheroma." | * |
| 5 | Lindeboom & Bouwer[6] (1949) | 23 | * | * | * | Past history noncontributory; severe precordial pain followed by cyanosis, hematemesis & death; blood pressure 160/90; rough pulmonic systolic murmur; blood urea nitrogen 73 mg./100 cc. | 2.5-cm. transverse intimal tear above aortic valve; dissection to 5 cm. below renal arteries; perforation into aortic lumen; "spotted" kidneys. | Intima normal; media showed focal mucoid degeneration; swollen endothelium of vasa vasorum; adventitia showed inflammatory changes; bilateral renal cortical necrosis. |
| 6 | Henley[7] (1951) | 46 | 3 | 1 | 9 | Past history of "mild toxemia" of pregnancy; sudden retrosternal pain radiating to jaw & right hip, with cyanosis of right leg & absent blood pressure in right arm; pain subsided & viable infant delivered by cesarean section; diastolic aortic murmur; death 2 days postoperatively. | At operation aneurysm extended to 2.5 cm. below diaphragm ("about twice size of normal aorta") | * |
| 7 | Griffiths et al.[8] (1951) | 34 | 4 | 4 | † | Past history noncontributory; sensation of "sinking" on 6th post-partum day; progressive dyspnea, with death 2 days later; patient's 14-year-old son died of dissecting aortic aneurysm. | Massive hemorrhage into abdominal cavity; dissection involved 1st 7.6 cm. of abdominal aorta; patches of atheroma in aorta. | * |

*Information not given.
†5th post-partum day.

## SUMMARY

The thirty-seventh reported case of dissecting aneurysm during pregnancy is presented. The previous finding that approximately 50 per cent of women

in whom a dissecting aneurysm develops before the age of forty were pregnant is confirmed.

We are indebted to Mr. James T. Deal for assistance in this study.

TABLE 1 *(Concluded).*

| CASE NO. | AUTHOR | AGE | GRAVIDITY | PARITY | MONTH OF PREGNANCY | CLINICAL DATA | GROSS AUTOPSY FINDINGS | MICROSCOPICAL FINDINGS |
|---|---|---|---|---|---|---|---|---|
| | | yr. | | | | | | |
| 8 | Furman et al.[9] (1952) | 27 | 2 | 1 | 2½ | Past history of migrating polyarthritis in childhood; precordial murmur in adult life; toxemia of pregnancy at age of 20, nephrolithotomy at age of 22, with blood pressure of 150/90; present illness consisted of dizziness & blurred vision, with blood pressure of 144/76 to 165/100; coarctation diagnosed by angiocardiography; abortion performed; thoracotomy for repair of coarctation, with incidental finding of aneurysm; patient alive 1 year later. | At operation coarctation found distal to left subclavian artery; bluish discoloration of proximal aorta; dissection at cut end of left subclavian artery; severe atherosclerosis of proximal aorta. | * |
| 9 | Spenser[10] (1952) | 32 | 3 | * | 8 | Past history noncontributory; 24-hr. history of increasing precordial pain radiating to neck & left arm; sudden death; blood pressure 106/50; loud systolic & diastolic murmurs; postmortem cesarean delivery of viable child. | Hemopericardium (400 cc.) with 2.5-cm. longitudinal intimal tear above left coronary ostium & with double-barreled aorta for 9 cm. | Media showed mucoid cystic degeneration |
| 10 | Hickey[11] (1953) | 29 | * | * | 8 | Past history noncontributory; severe pain in chest & back; sudden death 4 days later. | Hemopericardium (1000 cc.) with 4-cm. transverse intimal tear 2 cm. above aortic valve; dissection to just below renal arteries; scanty, small atheromatous flecks. | Intima normal; media showed increase in interlaminar connective tissue, which was partially hyalinized, vacuolated & cystic; adventitia showed inflammatory changes. |
| 11 | Weil et al.[12] | 42 | 4 | 3 | 7 | Past history noncontributory; pain at base of neck for 1 day; blood pressure 124/96; precordial systolic murmur; sudden death; cesarean section, with viable infant. | Hemopericardium; aneurysm began at 1st part of ascending aorta & extended to junction of transverse & descending aorta. | * |
| 12 | Sichel et al.[13] (1954) | 35 | 3 | 2 | † | Past history noncontributory; sudden substernal pain radiating to neck & arms on 5th post-partum day; blood pressure 188/88; loud systolic and harsh diastolic murmurs; sudden death. | Hemopericardium (750 cc.), with 3.5-cm. transverse intimal tear 1 cm. beyond left subclavian artery; minimal arteriosclerosis. | * |
| 13 | Mandel et al. (present case) | 20 | 1 | 0 | 4 | Past history of hypertension for 3 yr.; scarlet fever & "dropsy" in childhood; sudden onset of chest & back pain, with nausea & vomiting; loud systolic & diastolic aortic murmurs; blood pressure 248/142 in right arm & 230/80 in left arm; sudden death. | Hemopericardium (700 cc.), with 1.5-cm. T-shaped intimal tear 2 cm. above aortic valve; dissection to 4 cm. above iliac vessels & reperforation into aorta; early atherosclerosis | Intima showed early atherosclerosis; media showed mucoid cystic degeneration; adventitia showed inflammatory changes. |

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# CASE RECORDS
## OF THE
## MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

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## CASE 40511

### PRESENTATION OF CASE

A twenty-nine-year-old housewife, six months pregnant, was admitted to the hospital with a chief complaint of shortness of breath.

During the first three months of pregnancy the patient had a "cold" with coryza, nasal congestion and bright-red streaking of sputum. Nineteen days before admission she had a sudden onset of pain in the left side of the chest. Within a few minutes the pain became excruciating but abated somewhat when the area was rubbed. At this time she again spat up bright-red blood. The next day her physician sent her to another hospital. She was in acute respiratory distress. No breath sounds were heard over the entire left side of the chest, and x-ray examination revealed obliteration of the left lung. The hemoglobin at this time was 5.0 gm. per 100 cc., and the red-cell count 2,000,000. The urine was normal. In the other hospital the chest pain occasionally recurred but less severely. She noted some dyspnea. She received oxygen on admission and 2 units of whole blood. She was referred to this hospital for bronchoscopic examination.

The patient had had 5 normal full-term pregnancies. There was no history of exposure to tuberculosis. She had no other symptoms except occasional rectal bleeding attributed to hemorrhoids.

Physical examination showed a well developed, pale woman, with scleral icterus. Slight dyspnea was noted, and the trachea was shifted slightly to the right side. The left side of the chest was dull throughout, with bronchial breath sounds and decreased tactile and vocal fremitus. The heart was normal. The abdomen was enlarged. The liver edge was palpable 3 fingerbreadths below the right costal margin. On pelvic examination the cervix was soft, the uterus was extended to the umbilicus, and fetal parts were felt. One observer felt the tip of the spleen. There was slight tenderness over the fourth thoracic vertebra.

The temperature was 100.2°F., the pulse 100, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic.

The urine was amber and cloudy, contained a trace of sugar and gave a ++ test for acetone; microscopical examination of the sediment revealed 0 to 6 white cells and occasional red cells per high-power field. Examination of the blood disclosed a hemoglobin of 10.0 gm. per 100 cc., and a white-cell count of 14,600, with 71 per cent neutrophils, 15 per cent lymphocytes, 10 per cent monocytes, 2 per cent eosinophils and 2 per cent basophils. On the smear, the platelets were considered normal, and the red cells varied somewhat in size but were uniform in shape. The total serum protein was 7.0 gm., the albumin 3.4 gm., the globulin 3.6 gm., the nonprotein nitrogen 17 mg., the bilirubin 1.6 mg., and the alkaline phosphatase 4.6 units per 100 cc., and the sodium was 134 milliequiv., the potassium 4.6 milliequiv., and the chloride 99 milliequiv. per liter. Cephalin flocculation was negative in twenty-four and forty-eight hours. The prothrombin time was 13 seconds (normal, 13 seconds). The bleeding time was 3 minutes, and the clotting time 13 minutes. The urinary urobilinogen was 7.2 Ehrlich units. A stool was soft, brown and guaiac negative. X-ray films of the chest showed an expanding lesion in the posterior proximal portion of the left fifth rib, accompanied by a soft-tissue mass (6 cm. in diameter), and pleural effusion on the left. The mediastinum was displaced to the right (Fig. 1). X-ray films of the long bones revealed no destructive lesions in the bones of the forearms, upper arms, thighs or lower legs.

On the second hospital day a thoracentesis yielded 2700 cc. of grossly bloody fluid from the left side of the chest, with improvement of respiratory distress. Specimens submitted for cytologic and cell-block examinations were both negative for tumor cells. X-ray films taken after thoracentesis more clearly defined the mass mentioned above. The mediastinum was now slightly displaced to the left and was thought to indicate a certain degree of collapse of the underlying lung. On the third and seventh hospital days the patient was given transfusions of 500 cc. each. The hemoglobin was 12.0 gm. per 100 cc. On the eighth hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR. STANLEY M. WYMAN*: It seems to me that the chest pain and shortness of breath were quite separate from the six-month pregnancy. I tried to find some explanation for the coryza, nasal congestion and spitting of streaks of blood that occurred in the first three months of pregnancy and again toward the end of the history. I do not think I can relate it to the pregnancy. I wondered, however, if it was related to

*Radiologist, Massachusetts General Hospital.

the tumor in the left side of the chest, which may have been involving the lung at that time and causing hemoptysis. The anemia and icterus I think I shall have to account for on the basis of blood destruction. She did have an elevated urinary urobilinogen. I do not have further information about the blood studies.

The fluid in the left side of the chest is quite evident, and the displacement of the heart can be accounted for on that basis. That may also account for the palpable liver edge 3 fingerbreadths below the right costal margin. I should think that there was enough displacement to say that the liver was not enlarged, and there was no other evidence of liver disease. I think all these laboratory tests are noncontributory with the exception of the urinary urobilinogen.

Now I come to the crux of the matter as I see it, the x-ray examination of the chest. These films cover two successive days. As reported in the protocol, the initial films show density in the left side of the chest that is presumably fluid. The heart and mediastinum are displaced very considerably toward the right, the barium-filled esophagus being pushed over. The right leaf of the diaphragm lies very low, presumably because of compression of the lungs and the attempt of the right lung to take over the function of the collapsed left lung. There is an expanding lesion of the head of the fifth rib on the left. The lateral film adds very little at this time. A second film taken the same day with a good deal more penetration shows this expanded portion of rib much better (Fig. 1). The cortex is greatly displaced and is broken through in the bottom portion. One finding on these films that may be of significance is the definite suggestion of two or three small areas of calcification lying below the destroyed rib. After the removal of 2700 cc. of bloody fluid from the chest there is a fluid level in the apex of the chest with some air above it. This must represent a great deal of fluid in the left pleural space. Now a compressed left lung is seen. There is a soft-tissue mass that seems to be in continuity with or at least adjacent to the involved fifth rib. This is seen on all the films. In other words, this is probably a solitary lesion arising in the rib, expanding the rib, destroying the cortex, bursting out and forming a surrounding soft-tissue mass. In the other x-ray examinations, the other bones do not give any evidence of disease. I always worry about widespread bone-marrow disease if there is any degree of anemia, but I cannot establish it on the basis of the x-ray examination.

A wide range of possibilities may be offered in explanation of this solitary lesion. I think it is unnecessary to go through the congenital, infectious, traumatic and metabolic causes. I do not think this mass suggests any of those. It is possible that it was an eosinophilic granuloma, but I shall discard that at the moment.

This looks like a tumor, and I think it has the appearance of a malignant one. This is almost certain because of the grossly bloody pleural effusion and the profound anemia. Unfortunately, the chest tap did not give the answer histologically.

Among the benign possibilities chondroma, osteochondroma and giant-cell tumor should be mentioned. Chondromas and osteochondromas occur particularly where there is cartilage, more commonly in the outer ends than in the heads of the ribs. Giant-cell tumors may occur in this location or in the end of any long bone.

Among the malignant possibilities, I think one cannot exclude metastatic cancer, particularly from a

FIGURE 1. *Roentgenogram of the Chest.*
*There is massive accumulation of fluid in the left pleural space displacing the esophagus to the right. The arrow points to the expansile lytic lesion of the posterior aspect of the left fifth rib.*

renal-cell or thyroid carcinoma. However, there was no evidence for thyroid or renal disease, and I shall have to assume that these conditions did not exist although a small primary lesion could have been overlooked.

To turn to the primary malignant tumors, the sarcomatous counterpart of chondroma, osteochondroma and giant-cell tumor could produce this appearance. An osteogenic sarcoma should be considered, but it is most unlikely that it would look like this. An osteogenic sarcoma may be osteolytic or osteogenic, but it does not usually expand bone and produce a large surrounding soft-tissue lesion. Fibrosarcoma, not a very common tumor, can look very much like a giant-cell tumor. In other words, it can expand the cortex of bone, producing large crossing trabeculae and eventually breaking through the cortex in much this same fashion.

The two possibilities that I like best are Ewing's sarcoma and reticulum-cell sarcoma. I cannot distinguish these two conditions from one another or from several of the things that I have already mentioned. Both most commonly affect young persons, particularly Ewing's sarcoma, which occurs most often in the shaft of a long bone although it may occur near the end. Reticulum-cell sarcoma is more likely to occur in the end of a long bone. Each of these conditions may expand, thin and destroy the cortex. I do not know which to pick, but since I must choose one, I should favor Ewing's sarcoma.

The next question is, What should be done? I think that biopsy is the next logical step. This will, with a high degree of certainty, give the answer. Then the proper method of treatment can be carried out. If this patient had a reticulum-cell or a Ewing sarcoma I think she should have received radiation therapy as the method of choice. If she had a chondrosarcoma, fibrosarcoma or osteogenic sarcoma, I think surgical treatment should have been preferred.

DR. BERNARD M. JACOBSON: I think the examiner who could feel the spleen during the sixth month of pregnancy was very skillful. Would the splenomegaly veer you to either of those choices?

DR. WYMAN: I suppose if I could be sure of that it would veer me to lymphoma. However, with so much pleural effusion pushing the spleen down, in the same fashion that the liver was pushed down, a perfectly normal spleen may have been palpable.

DR. JACOBSON: May I amend your statement about the urinary urobilinogen? Only in unusually acute hemolytic anemia is the breakdown accompanied by a high urinary urobilinogen. Usually, the value rises only when there is liver dysfunction. That might possibly lead one to think that the liver was involved in the disease.

DR. ALFRED KRANES: Is there not a good deal of controversy about the accuracy of that procedure?

DR. JACOBSON: I presume that this was the two-hour test done by Dr. Chester M. Jones's laboratory; normally, it is up to 1.3 Ehrlich units.

DR. JOHN D. STOECKLE: I wondered if Dr. Wyman would consider a hemangioma of the rib, with rupture and invasion rather than effusion due to pleural involvement.

DR. WYMAN: Yes; I think that is a good possibility.

A PHYSICIAN: Could it have been a myeloma?

DR. WYMAN: In my experience, myeloma does not expand a long bone to this degree.

DR. BENJAMIN CASTLEMAN: If a myelomatous lesion had expanded the bone and then broken through, would not the picture be like this?

DR. WYMAN: It is possible, but myeloma is predominantly a bone-destructive process.

DR. LAURENCE L. ROBBINS: I should like to emphasize one point. I certainly agree that we cannot differentiate the exact process that is going on here. I further agree, and I thought at the time, that this was a malignant tumor, but I should go a little farther with Dr. Wyman's statement about the biopsy and say that I think the pathologist ought to have the opportunity to study a frozen section during the time of the biopsy. In the cases in which he can be certain, a decision can be made then and there about whether radiation therapy or a more complete surgical procedure is necessary.

DR. CASTLEMAN: Ordinarily, that is a good procedure to follow. However, if this were a chondrosarcoma that had not ruptured, one would hesitate to biopsy it because of the danger of implanting cartilaginous cells.

DR. ROBBINS: How, without a biopsy, would you differentiate Ewing's or reticulum-cell sarcoma from the chondrosarcoma that does not produce calcification? Certainly, Ewing's tumors, which have been confused with cartilaginous lesions and have had resection or removal of the entire rib, have been disastrous as far as the ultimate fate of the patient is concerned.

DR. CASTLEMAN: It might be very difficult. However, most cartilaginous tumors can be recognized grossly at the time of operation.

It is interesting that the official diagnosis from the Department of Radiology was exactly the same as Dr. Wyman's — Ewing's sarcoma first and reticulum-cell sarcoma second. The fourth-year students called this tuberculosis of the fourth rib, with hemorrhage into the pleura. Do you have any comment on that?

DR. WYMAN: I hope it was not tuberculosis because I did not mention that possibility. I think the appearance would be most unusual; I do not recall seeing such a picture with tuberculosis.

DR. EDWARD B. BENEDICT: The patient was sent to me by her physician primarily for bronchoscopy, without any information or any x-ray reports. I think it is worth emphasizing that even though there is hemoptysis, we do not always proceed right away with a bronchoscopy. This patient was much too sick for bronchoscopy so we did further studies first and found that bronchoscopy was not indicated at all.

DR. WALTER E. KLINGENSMITH: The exploration was made through the rib below the one in which the tumor was situated. When the chest was opened an organized hemothorax, which had prevented expansion of the lung, was found. The tip of the lower lobe was fastened against the tumor. The tumor itself was reasonably hard and bled on the slightest touch. It expanded the rib and also produced a large mass, as seen in the x-ray film, which lay against but did not actually invade the head of the transverse process of the vertebra. A wide resection of the tumor was performed; the entire length of the involved rib and approximately half the portions of the ribs above and below it were removed. This was taken in extraperiosteal fashion, and a plastic closure was performed. Also, the transverse process of the involved vertebra was excised.

### Clinical Diagnosis

?Ewing's sarcoma.
?Reticulum-cell sarcoma.

### Dr. Stanley M. Wyman's Diagnosis

?Ewing's sarcoma.
?Reticulum-cell sarcoma.

### Anatomical Diagnosis

*Benign giant-cell tumor of rib.*

### Pathological Discussion

Dr. Castleman: The tumor was very hemorrhagic and had yellowish and grayish areas and a few tiny spicules of bone scattered through it. Microscopical examination showed a very characteristic giant-cell tumor, with giant cells and characteristic stromal cells (Fig. 2). These cells were small and innocuous looking. I do not believe we saw any mitotic figures. The giant cells looked like those seen in the ordinary benign giant-cell tumors. As Dr. Wyman said, this was one of the benign lesions that produce marked expansion, which would go along with his thought that it was a slowly growing lesion that finally did rupture.

There were two other lesions that we considered: the hemangioma mentioned by Dr. Stoeckle — this certainly was not that — and the aneurysmal bone cyst, a lesion that has recently been described by Lichtenstein.[1] The aneurysmal bone cyst could, I suppose, produce a picture not unlike this. That lesion often has giant cells in the region of the hemorrhage, but it also has large vascular spaces, which were not present in this particular case. I do not think there is any question that this was not a giant-cell tumor.

When the patient returned to the Out Patient Department, six weeks after operation, she felt well and apparently was still pregnant. The x-ray films of the chest revealed slight blunting of the left costophrenic angle; with the allowance for some difference in technic there has been further clearing in the lung field.

Dr. Kranes: Was the hemoglobin determined on the later visit?

Dr. Castleman: No.

Dr. Jacobson: What is the prognosis?

Dr. Castleman: I think the prognosis should be good. About 10 per cent of the giant-cell tumors do recur. Of course, since this tumor broke through the cortex, there may be a recurrence. I do not believe x-ray therapy is called for. Most of the giant-cell tumors that become malignant years later have received x-ray treatment. In the series recently reported from the Mayo Clinic[2] I believe that all the cases that went on to sarcomatous change had received radiation. There may be a definite correlation between the institution of radiation and the development of the sarcoma.

Dr. Robbins: I should also withhold the radiation, but I am not convinced yet that it is the etiologic factor in the development of sarcoma because we have seen some malignant giant-cell tumors that have had no radiation.

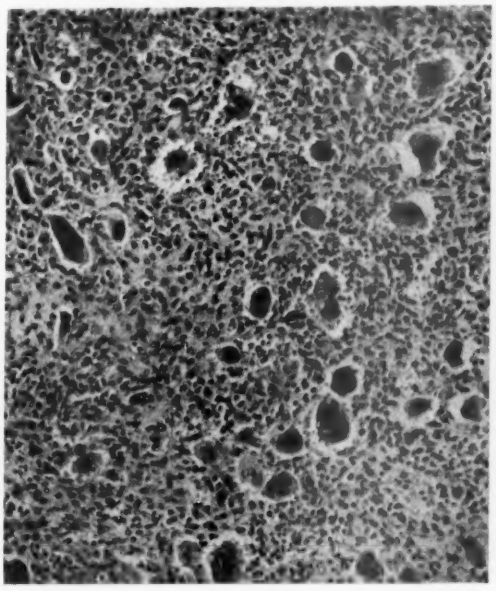

Figure 2.

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## CASE 40512

### Presentation of Case

A forty-nine-year-old chemist entered the hospital because of cough and weakness.

Eleven months previously he began to notice general malaise, anorexia and weight loss, which were attributed to poor teeth, and a complete extraction was done but without benefit. Shortly thereafter, he also began to have loose stools, with five or six bowel movements a day, which decreased to twice a day about two weeks before admission. Two months before admission, he awoke in the morning with severe pain in the left side of the chest anteriorly; this was associated with cough productive of thick, yellow-brown phlegm. His physician treated him with chlortetracycline for four days; this gave some relief from the chest pain but not from the coughing. Since then he had felt weak, and was dyspneic on climbing half a flight of stairs. He lost 29 pounds in weight. The

chest pain on coughing was severest when he was lying supine and least severe when he was lying on the right side. There was no wheezing or hemoptysis. He had been smoking 1 package of cigarettes a day for thirty-two years. An upper gastrointestinal series was normal. A roentgenogram of the chest at a county sanatorium one month before admission revealed a large area of increased density in the left-middle-lung field, and a second film eighteen days later showed some progression of the lesion. A tuberculin

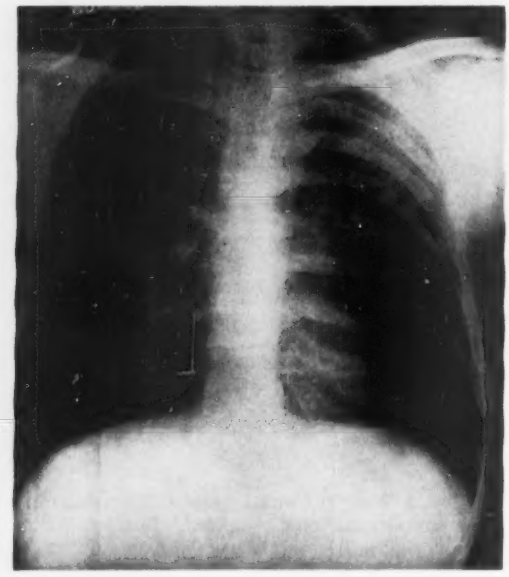

FIGURE 1. *Posteroanterior Roentgenogram of the Chest, Showing the Consolidative Process in the Left Upper Lobe.*

test was negative, and examination of the sputum disclosed no acid-fast organisms.

He had had "pneumonia" twenty-three years before admission. The past history was otherwise noncontributory.

Physical examination revealed a well developed but poorly nourished, pale man who appeared to be in no acute distress. The lungs were clear, and the heart normal. The abdomen was soft, and no masses could be felt. Rectal examination was negative.

The temperature was 100.5°F., the pulse 90, and the respirations 20. The blood pressure was 110 systolic, 70 diastolic.

Urinalysis was negative. Examination of the blood showed a hemoglobin of 9.5 gm. per 100 cc. and a white-cell count of 11,550. The serum total protein was 6.4 gm., with an albumin-globulin ratio of 1.6, and the nonprotein nitrogen 27 mg. per 100 cc. Culture of the sputum grew out *Staphylococcus albus, Staph. aureus* and alpha-hemolytic streptococcus. Six cytologic studies of the sputum were either unsatisfactory or doubtful. The roentgenogram of the chest revealed an irregular density in the left-upper-lung field peripherally that had indistinct margins and was connected to the left hilar region by irregular strands of density (Fig. 1). It seemed to be situated mostly in the posterior and lateral parts of the left upper lobe although a small triangular density was seen in the anterior segment as well. At the inferior margin of the lesion there were translucent areas of various sizes. The trachea was in the midline, and the left main bronchus was patent. Irregular strands of infiltration were also seen extending from the left hilus down into the left-lower-lung field. At the left cardiophrenic angle there was a round density with indistinct margins, measuring approximately 3.5 cm. in its greatest diameter. No active disease was seen in the right lung. There were no enlarged mediastinal lymph nodes, bone destruction of the ribs or fluid in the pleural spaces. The Graham–Cole test and a barium-enema examination were negative. On bronchoscopy, a large amount of white secretion was seen coming from the left-upper-lobe orifice, and the apical anterior segmental bronchus appeared narrowed, probably from extrinsic pressure.

The patient ran a low-grade fever, with temperatures between 99 and 100°F. On the eighth day, an operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR. KENNETH T. BIRD*: This patient began to note vague complaints eleven months before admission. These consisted of malaise, anorexia and weight loss, which eventually amounted to the considerable figure of 29 pounds. Focal infection of the teeth was the presumed cause, but, as so frequently happens, extractions produced no relief of the symptoms. Painless diarrhea began shortly after the onset of the nonlocalizing complaints. For the first time attention can be given to a specific organ system. I shall assume that the stools presented no outstanding feature since no description is available in the protocol. Accordingly, I can only conclude that the patient had chronic diarrhea, which diminished despite the sudden involvement of a second organ system.

The acute onset of pain in the left side of the chest, with cough productive of thick yellow-brown phlegm, signaled the onset of the pulmonary disease, which promptly became the chief problem and the target of the therapeutic attack. The development of pleuritic pain with the simultaneous onset of cough and sputum is consistent with a pneumonia. This may be an unrelated interim process caused by the general debility or one directly associated with an underlying disease. In any event, the pulmonary symptoms dominated the clinical picture and could have been due to the sudden development of a pneumonic process in a previously uninvolved lung or an exacerbation of an underlying parenchymal disease. I shall return to consideration of this second possibility in a moment.

*Assistant in medicine, Massachusetts General Hospital.

The description of the sputum as thickened and yellow brown does not help much. The brownish color suggests the presence of changed hemoglobin in small amounts. Incidentally, the common green color of sputum is probably due to green pigment, appropriately called verdoperoxidase, which is liberated on the disintegration of granulocytes. This enzyme accumulates when secretions stagnate within the tracheobronchial tree. Presumably, no stagnation of secretions was present within the tracheobronchial tree of this patient particularly since a large number of white secretions coming from the left-upper-lobe orifice were seen through the bronchoscope. One final word about sputum. Sputum is best observed not deep within a waxed cardboard box with inverted flaps, which effectively conceal its nature, but in a clear-glass container. A three-layered sputum with mucus above, sediment below and a watery intermediate layer is characteristic of active pulmonary suppuration with parenchymal destruction. I think I could profit from a better gross description of the sputum, but it is not available.

To consider in more detail the specific pulmonary diagnosis, an infectious process or a neoplasm could first become manifest in the gastrointestinal tract and later in the lungs. Review of the barium-enema examination may be helpful. But before the x-ray films are reviewed the apparent relief of the acute pleuritic chest pain coincident with chlortetracycline therapy is worthy of comment. Since I cannot be certain whether the response was specific or merely coincidental, I suspect that the transient acute pleurisy cleared spontaneously and was unrelated to drug therapy.

It is interesting to speculate why the patient was least comfortable in the supine position. This may mean that he had a focus of disease far anteriorly in the upper lobe that was immediately beneath the pleura. In the supine position more local traction is possible through pleural adhesions. Perhaps the x-ray films of the chest or the operative findings will give the answer since I believe a thoracotomy, with resection of the upper lobe on the left, was performed.

I should like to review the available x-ray films.

Dr. John F. Gibbons: The first available chest films were made elsewhere about two weeks before admission to this hospital, and on these films one can see what appears to be a more or less homogeneous area of consolidation with ill-defined edges extending peripherally from the hilar area outward into the upper lobe posteriorly. At that time, the lateral view reveals no consolidation in the anterior segment of this lobe, and the lower lobe is apparently clear except for some prominence of linear markings adjacent to the left border of the heart. The rib cage appears to be intact, and the heart is not enlarged. The next films were made here shortly after admission, and by means of overexposed grid films one can see dilated bronchi extending into the area of infiltration previously described; moreover a small area of infiltration has appeared in the anterior segment of the left upper lobe (Fig. 1). The trachea is in the midline, and the major bronchi appear patent. The density described in the protocol at the left cardiophrenic angle is not very impressive and may represent only conglomerate rib and vascular shadows. There is no evidence of pleural effusion.

A review of the cholecystogram and the barium-enema films reveals only that there was some slight change in the mucosa of the distal large bowel.

Dr. Bird: Is the lower lobe of the lung free of disease?

Dr. Gibbons: Yes; I believe the lower lobe of the left lung is probably free of disease.

Dr. Bird: Is cavitation present, or are the translucent areas due to bronchiectasis?

Dr. Gibbons: The translucent areas in the consolidated portion of the left upper lobe are probably due to dilated bronchi (bronchiectasis), and I do not think that cavitation is present.

Dr. Bird: Were studies done to determine whether or not the carinal lymph nodes were enlarged? What is the value of this study?

Dr. Gibbons: It is our usual routine to perform fluoroscopy on all patients with findings such as these and to search for enlargement of the mediastinal and carinal lymph nodes by means of appropriate spot films and barium swallow, since these nodes may only indicate their presence by localized indentation on the barium-filled esophagus. It is important to demonstrate these lymph nodes not only to delineate the entire extent of the pathologic process but also to differentiate neoplasm from infection and thus help the surgeon decide on his method of approach when pneumonectomy or lobectomy is contemplated. Moreover, inoperability of a malignant process can often be determined before thoracotomy by these methods. Apparently, a barium-swallow examination was not done to search for enlarged lymph nodes. The routine and grid films of the chest give no evidence of enlargement of the subcarinal or mediastinal lymph nodes.

Dr. Bird: What is the purpose of lordotic views in various degrees of obliquity?

Dr. Gibbons: Lordotic views in various degrees of obliquity are sometimes helpful in delineating narrowed bronchi and may aid in visualizing lesions that are partially hidden by the overlying clavicle or anterior ribs.

Dr. Bird: In a lung that showed such extensive infiltration on x-ray study I am hard pressed to explain why no single abnormal finding was demonstrated. (Not even the smallest rale!) I believe that, if we all practiced the "Listen, Look, Re-listen" technic of chest examination, the diagnosis of many chest diseases would be on a sounder clinical basis. By this I mean that, after careful physical examination of the chest ("Listen") and after an equally care-

ful examination of the chest film ("Look"), assisted by an expert such as I have had just now, the clinician would do well to re-examine the chest ("Relisten") with all the available information that the chest film can provide about the nature and localization of a lesion or lesions.

The first chest film was taken when the patient was referred to the diagnostic clinic of a county sanatorium, where he was seen as an outpatient. I was present at the sanatorium staff conference when his pulmonary problem was originally reviewed. It was then believed that prompt bronchoscopic examination was indicated because the clinical suspicion of tumor was great. Furthermore, two sputum specimens were negative on concentration smear. At this time the tuberculin test was found to be negative to 0.1 mg. of Old Tuberculin but was + + + to 1 mg. of Old Tuberculin. There is, then, a degree of inaccuracy in the protocol: "A tuberculin test was negative." This discussion about the tuberculin test may seem like a minor detail, but for all practical purposes the diagnosis of active pulmonary tuberculosis cannot be made unless the tuberculin test is positive. To be called "negative" I believe the tuberculin test must be done not only with 0.1 mg. of Old Tuberculin (1:1000 dilution) in the standard volume of 0.1 cc. but also with 1 mg. (1:100 dilution) if the weak or 0.1-mg. test is negative. It is of interest that a small but definite group of patients with active pulmonary tuberculosis will react only when tested with a full 1-mg. dose of Old Tuberculin intradermally. However, I will grant that so-called tuberculin-negative tuberculosis may be present during the incubation period of primary tuberculosis, in association with an overwhelming infection, in cachexia and during the course of certain nontuberculous infectious diseases, particularly measles. This patient had none of these conditions. Accordingly, on the basis of the clinical, x-ray and bronchoscopic findings he could have had tuberculosis.

Tuberculosis can mimic virtually any pulmonary disease, but it is equally true that many pulmonary diseases can mimic tuberculosis. An acute suppurative or necrotizing pneumonia could have been present in the case under discussion. The extent of the disease widely scattered throughout the left upper lobe excludes a hematogenous origin. Aspiration of infected material can produce a so-called bronchial embolus. If suppurative organisms are present, an intense alveolar reaction follows when such an infected embolus lodges within a segmental bronchus. The left upper lobe is not an uncommon site for acute suppurative disease. In fact, as many as 1 out of 5 lung abscesses occur in the left upper lobe. In either lateral decubitus position the corresponding upper-lobe bronchus is in a completely dependent position. Thus, the mechanical arrangement is ideal for the localization of a bronchial embolus within an upper-lobe bronchus or within the segmental bronchi of the upper lobe. This patient, already debilitated from a chronic diarrhea, could have aspirated infected material into the left-upper-lobe segmental bronchi with the production of acute suppurative disease. The short course of chlortetracycline may have relieved the acute symptoms and even allowed some organization of the pneumonic process to occur. Although such a condition could have been present I am willing to put it as an alternate diagnostic possibility.

A wide variety of specific organisms can cause chronic suppurative disease. Staphylococci and streptococci, aerobic and anaerobic, are perhaps the commonest. I shall exclude pneumonia due to Friedländer's bacillus because of the failure to identify the organism on smear or culture. Certain fungous diseases, especially histoplasmosis, blastomycosis and actinomycosis, could give this clinical picture. All require a high degree of diagnostic suspicion on the part of the physician as well as careful laboratory study.

In view of the increasing awareness of chronic interstitial pneumonitis associated with intracellular lipid deposition I must mention this condition briefly. This follows a respiratory illness that is usually of acute onset but may be insidious. The diagnosis can only be suspected by the clinician. No findings except those supplied by the pathologist are diagnostic. Persistence of cough, sputum and respiratory symptoms in conjunction with chronic, localized and unchanging x-ray findings in a lobe that is reduced in size are characteristic. But these findings are associated with practically any localized chronic pulmonary disease. This entity should not be confused with aspiration lipid pneumonia or so-called lipoid pneumonia or paraffinoma; it is unfortunate that these diseases of different origin have such similar names. Chronic interstitial pneumonitis with intracellular lipid deposition, alias cholesterol pneumonitis, is, in the laboratory animal at least, the end result of local tissue factors, chiefly lowered pH. A recent excellent paper by Waddell, Sniffen and Whytehead,* of this hospital, describes the etiology of this interesting pulmonary disease.

In closing I shall consider carcinoma of the lung. To explain the apparent lobar distribution of the disease a primary neoplasm should be located within the lobar bronchus. Only the outermost margin of the left upper lobe is visible through the standard bronchoscope. Sometimes, in fact, only the distal spur can be seen. Hence, unless the right-angle telescope was used for inspection of the lobar bronchus itself I cannot be certain that a neoplasm within the upper lobe can be excluded. Since there is no apical anterior segmental bronchus on the left, this is probably a misprint; I wonder whether both aspects might be checked. Was the right-angle telescope used to evaluate the left-upper-lobe orifice, and exactly what segmental bronchus was narrowed?

*Waddell, W. R., Sniffen, R. C., and Whytehead, L. L. Etiology of chronic interstitial pneumonitis associated with lipid deposition: experimental study. *J. Thoracic Surg.* **28**:134-144, 1954.

DR. EDWARD B. BENEDICT: Dr. James M. Shannon and I did this bronchoscopic examination together, and we did use the right-angle telescope. There was an error in the dictation or in the transcribing, and I cannot remember now whether there was narrowing of the anterior segmental bronchus or the apical posterior segmental bronchus, or possibly both. We thought the narrowing was mostly due to extrinsic pressure, but some intrinsic irregularity may have been present. The conclusion was "partial occlusion probably due to tumor." We have, however, seen extrinsic pressure with this appearance in tuberculosis or pneumonitis.

DR. BIRD: Since the left-upper-lobe bronchus was normal on telescopic examination I believe bronchogenic carcinoma can be excluded. Yet I shall have to admit that alveolar-cell carcinoma, pulmonary adenomatosis or even a multicentric peripheral bronchogenic carcinoma could cause this clinical picture. Since the cytologic study of the sputum did not show tumor cells and since I find "doubtful" reports of no clear-cut value I shall exclude carcinoma. Too often doubtful reports cause fulminating cancer phobia on the part of the physician. I believe this patient had chronic pulmonary suppuration, which is most consistent with tuberculosis. Chronic nontuberculous pulmonary suppuration is my alternative diagnosis.

DR. RICHARD B. COHEN: Dr. Grillo, will you tell us the opinion on the ward before operation?

DR. HERMES C. GRILLO: Despite the bronchoscopic findings we believed that carcinoma with suppuration behind it was most likely, although our suspicion of chronic inflammatory disease alone was great. We did not think that tuberculosis, although possible, was responsible for this process.

### CLINICAL DIAGNOSIS

Carcinoma of lung, left upper lobe.

### DR. KENNETH T. BIRD'S DIAGNOSIS

Chronic tuberculous pulmonary suppuration.

### ANATOMICAL DIAGNOSIS

*Chronic organizing pneumonitis, with foci of acute inflammation and abscess formation.*

### PATHOLOGICAL DISCUSSION

DR. COHEN: Will you describe the operative findings?

DR. GRILLO: The left upper lobe was densely adherent to the lateral parietal pleura. The lobe was consolidated in the apicoposterior and superior lingular regions and another firm area was present in the inferior lingula. To remove the lobe without entering what was evidently an inflammatory mass, we had to seek the extrapleural parietal plane in part. A small amount of thick purulent material escaped where the upper lobe was separated from the lower lobe. The lymph nodes were large. The lower lobe was normal.

DR. COHEN: As indicated by Dr. Grillo the pleura was generally thickened, and numerous adhesions were noted on the posterior surface. The bronchi gave no evidence of obstruction by tumor, but the walls were thickened and the mucosa reddened by what was apparently an inflammatory process. The parenchyma was extensively consolidated, and the process seemed most severe in the apicoposterior segment and adjacent areas. On section this portion of the lung was solid, gray and granular, with several areas of yellowish softening.

On microscopical study the process was in various phases of development. Large areas were typical of an acute bronchopneumonia with alveoli filled by neutrophils and preservation of alveolar walls. This process graded into abscesses with necrosis of alveolar walls and exudate. In other areas the changes were chronic, and characterized by both interstitial and septal fibrosis with fibrous organization of intra-alveolar exudates. Some smaller bronchi were dilated, and most were involved by the acute and chronic inflammatory process. The major portions of the anterior segment and lingula were free of inflammation. One solitary abscess surrounded by relatively normal parenchyma was present in the tip of the lingula. It measured 1.5 cm. in diameter and extended to the pleural surface. Patchy foci of emphysema were distributed throughout the lung and were prominent subpleurally. *Staph. albus* and *aureus,* alpha-hemolytic streptococci and abundant diphtheroids were cultured. No evidence of tuberculosis or tumor was found.

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## HEMISPHERIC MALARIA ERADICATION

THE World Health Organization of the United Nations, in the few years of its existence, has become accustomed to doing things with almost total effectiveness and accomplishing results by wholesale. Notable among these achievements have been its signal success in combating cholera wherever cholera has existed; its virtual eradication of yaws in Haiti; the B. C. G. vaccination of many millions of persons in a number of countries; its unremitting battle against syphilis and its exhaustive studies of those toxicologic problems of mankind — snakebite and alcoholism.

Having concerned itself long with man's most widespread plague, malaria (mosquitoes figured largely among the escapees from Pandora's box), the Organization has now developed a program to eradicate this disease from the entire Western Hemisphere. This will indeed be pouring oil on the troubled waters on a grand scale, although the principal factor in the campaign in the Americas will be the spraying of houses with such residual insecticides as DDT, which for months maintains its lethal effectiveness against the adult mosquito.

Much has already been accomplished since the Pan American Sanitary Bureau was founded at the first International Sanitary Conference of the American Republics, held in Washington in 1902. The United States is virtually malaria free except possibly for some counties in oil-bearing Texas, of all places, and malaria has been eradicated from five provinces in Argentina and three in Ecuador.

Emphasis, according to a release from the Office of Public Information of the Pan American Sanitary Bureau, is now placed on the thesis that malaria eradication can no longer be considered a local or national problem but must be undertaken on a continental scale. So long as any endemic areas remain, a threat to the entire hemisphere persists.

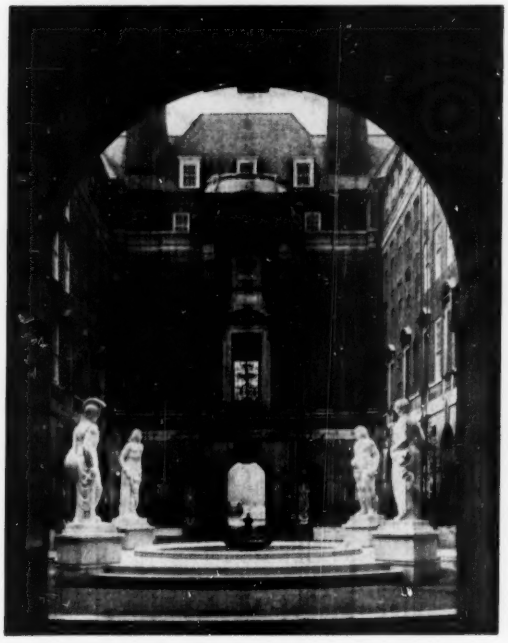
## BRITISH MEDICAL WAR MEMORIAL

NEARLY thirty years ago the new British Medical Association House in Tavistock Square, London, was formally opened by King George V and Queen Mary. At that time the Gates of Remembrance, leading to the Court of Honour, were dedicated as a memorial to the 574 members of the Association who had fallen in the first world war.

The Court of Honour itself, however, now cloistered by the enveloping wings and the great hall of the building, remained little more than a grassy plot of ground until another tragic war provided the occasion for its permanent enrichment. This has been achieved, as reported in the *British Medical Journal* on November 6, by the erection of a sculptured memorial, dedi-

cated by the Archbishop of Canterbury on November 2 to the medical men and women of the British Empire and Commonwealth who gave their lives in World War II.

The memorial that honors this larger group of nearly a thousand professional colleagues, 542 of whom were members of the Association, consists of a central fountain with four heroic-sized figures at its periphery and a bronze fountain jet resembling the



staff of Aesculapius at its center. The statues have as their themes Sacrifice, Cure, Prevention and Aspiration. Sacrifice is represented by Machaon, the legendary son of Aesculapius and a surgeon in the army of Agamemnon, struck by an arrow at the siege of Troy. Cure symbolizes the post-Greek eras of medicine and consists of a figure holding a lancet in the right hand. It is accompanied by two smaller figures, one bearing a dish to receive the blood from cupping, the other a drill such as was once used for trepanning; at the base of the group a mandrake grows.

The third symbolic figure, Prevention, dressed as of Jenner's period, holds an early form of microscope and is accompanied by a dog and a sheep representing the sacrificial animals of medical science. Aspiration, an idealized representation of Motherhood, leads a child hopefully into the uncertain future.

The memorial plaque bears the inscription:

> In Memoriam 1939 - 1945
> In Honour of the Medical Men and Women of the British Empire and Commonwealth of Nations who gave their lives in the Second World War.

"For here indeed," the Archbishop concluded his brief address, "is the law of life, the law of Christ, the law of God. 'Whosoever shall lose his life and throw it away for My sake and for the gospel's and for the service of others shall keep it unto life eternal.' "

## SAMUEL A. LEVINE PROFESSORSHIP OF MEDICINE

HARVARD University announced in November the establishment of the Samuel A. Levine professorship of medicine in the Harvard Medical School. This new professorship is a result of the generosity of Charles E. Merrill, a New York banker, the son of a physician, and a patient and personal friend of Dr. Levine.

In announcing the endowment of the new chair Dr. George P. Berry, dean of the Faculty of Medicine, said in part:

> The Samuel A. Levine Professorship is a symbol of the patient-doctor relationship on the frontiers of medical practice. It will provide new strength for the interrelations that have proven so fruitful in Dr. Levine's own work — the joining together of the practice of medicine, the medical school and the teaching hospital in the creation of knowledge and its perpetuation in future generations of doctors.

Mr. Merrill, whose economic success has been the means of implementing his social consciousness, is known for the diversity of his philanthropies. Educational institutions have particularly benefited from his intelligently administered generosity, which has been extended also to a variety of religious organizations—Catholic, Jewish and Protestant. Through the Merrill Foundation for Advancement of Financial Knowledge, research activities have been supported at the Harvard Business School, the Harvard School of Public Administration, Leland Stanford University, the University of Pennsylvania, the Massachusetts Institute of Technology and the Brookings Institution.

Dr. Levine is so well known in the world of medicine that his personal qualifications and his career need only brief mention in these columns. Born in Lomza, Poland, on January 1, 1891, he was brought to this country at the age of three; when he was eight years old he had already reached the sixth grade. A Boston newsboy, he received the second Harvard scholarship set up by the Newsboys' Union. He graduated from Harvard College in 1911 at the age of twenty, and from the Harvard Medical School three years later.

Specializing in cardiology, Dr. Levine was one of the first to appreciate the existence and the significance of coronary thrombosis. Associated principally with the Peter Bent Brigham and Beth Israel hospitals, Dr. Levine is clinical professor of medicine at the Harvard Medical School. A prolific writer, his major work has been *Clinical Heart Disease*, a textbook published in 1936 and now in its fourth edition. *Current Concepts in Digitalis Therapy*, by Bernard

Lown and Levine, ran through three issues of the *Journal* early in 1954 and has since been published in book form by Little, Brown and Company.

## DERMATOLOGIC STUDY AT TUFTS

An interesting academic development is suggested in the announcement by the Graduate School of Tufts College of the establishment of a two-year course in dermatology, leading to the degree of Master of Science. The course will be given at the Boston City Hospital under the direction of the physician-in-chief for diseases of the skin, Dr. Bernard Appel, and by members of his staff. Although the course is offered by the graduate school it is integrated with Tufts College Medical School through Dr. Appel, professor of dermatology and syphilology and chairman of the department.

This unusual departure in medical pedagogy, with its advanced academic standing, is available to candidates who can satisfy the admission requirements of the graduate school, which include the bachelor's degree in arts or sciences, and who hold appointments on the resident staff in dermatology at the hospital. The general purpose of such study is "to provide selected candidates an opportunity to better equip themselves for teaching and research while they are fulfilling the requirements for certification in this specialty."

The program of study will be divided into four parts. These will include a ten-credit course on the basic sciences as applied to dermatology, a ten-credit course on the fundamentals of dermatology, a series of weekly seminars adding up to four credits, and the completion of an original investigation with the preparation of a thesis.

Such attempts at co-ordination between the various schools of a university are encouraging to those who are interested in the breadth as well as the depth of education.

*A Dr. Thompson was lately hung in effigy at Richmond and Petersburg, Va., but for what cause we are unable to learn.*

Boston M. & S. J., *Dec. 27, 1854*

## MASSACHUSETTS MEDICAL SOCIETY

### *SIGILLUM SOCIETATIS*

The seal ("little signature") of the Massachusetts Medical Society is a figure of Aesculapius in his proper habit pointing to a wounded hart nipping the herb proper for his cure, with the motto *Natura duce*.

The skill of those commissioned to design such a seal during the past hundred and seventy-two years has been variable. The design in longest continuous

FIGURE 1. *Seal Designed by John R. Penniman in 1814.*

use, drawn by John R. Penniman in 1814, appeared on the official diploma of fellowship for eighty years (Fig. 1).

The earliest crude form of the seal, actually employed to impress a wax wafer, was in use from 1782

FIGURE 2. *Photograph of the Original Seal of the Society (in Use from 1782 to 1814).*

to 1814; its designer is deservedly anonymous (Fig. 2). Animated by a desire for authenticity and a reverence for the antique, however ugly, the secretary of

FIGURE 3. *Example of Redrawn Seal.*

the Society in 1916 exhumed this relic from the basement vault and had it carefully and exactly duplicated for embossing purposes. The Society has continued its use for thirty-eight years, for these things have an interminable life span, and it would be uneconomical to dispose of it.

However, it frequently becomes necessary to redraw the seal for purposes of reproduction on diplomas, stationery, pamphlets and so forth. Little thought has been given to the selection of a competent artist. The results have been at best commonplace, and occasionally repulsive (Fig. 3-5).

FIGURE 4. *Further Example of Redrawn Seal.*

Members of the Massachusetts Physicians Art Society and professional artists are cordially invited to reinterpret the conception of the founding fathers.

Attention is called to the facts that Aesculapius was a Greek; that there is no tradition of his being a chondrodystrophic, bald-headed old man with a beard; that the serpent clinging to his staff might well show

FIGURE 5. *Redrawn Seal, Showing Inferior Draftsmanship.*

more signs of animation than the usual formal caduceal figures; that the wounded hart is *Cervus elaphus* and bears antlers, not leaf-sprouting broomsticks, on his head and is not otherwise grotesquely deformed; that some thought might be given to the herb proper for his cure; and, finally, that it is not required that the motto be stamped on a ribbon floating in the sky.

Designs may be submitted to the secretary of the Massachusetts Medical Society, 22 Fenway, Boston 15.

## DEATH

LEARY — Timothy Leary, M.D., of Jamaica Plain, died on November 16. He was in his eighty-fifth year.

Dr. Leary received his degree from Harvard Medical School in 1895. He was emeritus professor of pathology, bacteriology and medical jurisprudence, Tufts College Medical School; formerly, medical examiner in Suffolk County; a member of the American Association of Pathologists and Bacteriologists and the Society of American Bacteriologists; and a fellow of the American Medical Association.

He is survived by his widow and two daughters.

# CIVIL DEFENSE AGENCY

## EMERGENCY IMPROVISED HOSPITAL PLANNING IN MASSACHUSETTS

Many existing hospitals of the Commonwealth are located within critical target areas and would probably be rendered inoperable in the event of a large-scale disaster such as an enemy attack. It is therefore imperative, in long-term disaster planning, to exclude the available hospital bed space in critical target areas. A step toward the solution of the ensuing problem is the development of an improvised hospital system that makes maximum use of existing facilities. This improvised hospital system will ultimately be composed of 200-bed units, which will provide early hospitalization for casualties in the vicinity of disaster areas.

In assessing the magnitude of the problem that confronts this emergency hospital system, one should consider existing designated critical target areas in the Commonwealth and the estimated number of surviving casualties to be expected therefrom. The total number of casualties needing immediate hospitalization and the type of casualty most likely to be encountered may be calculated from a knowledge of the type of bomb used and the point of detonation.

To meet the direct needs of hospitalization in a large-scale disaster a survey has been made of all public buildings throughout the Commonwealth capable of being converted into hospitals. This survey takes into consideration all schools, auditoriums, gymnasiums, halls and churches, together with their facilities that would be of assistance for conversion into an improvised hospital system. Approximately 1600 public buildings were chosen throughout the Commonwealth for this system.

Hospital bed space available in the Commonwealth is shown in Table 1.

TABLE 1. *Existing and Potential Hospital Bed Space in Massachusetts.*

| BED CAPACITY | NO. OF BEDS |
|---|---|
| Existing | 64,512 |
| Expanded | 75,928 |
| Improvised | 316,262 |

Seven 200-bed improvised hospital units have been purchased by Massachusetts. One 200-bed improvised hospital unit can be installed in any suitable large public building, and a space of approximately 15,000 square feet is required for each unit. It may be installed in any suitable location for immediate use by 30 trained personnel and auxiliaries in approximately four hours. This hospital will be mobile and will thus

greatly facilitate existing hospital and medical planning based on the fundamental principle of dispersal. The particulars of the hospital unit are designed on the principle of the 60-bed mobile army surgical hospital, which effectively provided surgical care for seriously wounded casualties at the front lines of combat in the Korean conflict.

The improvised hospital is composed of 288 different types of equipment including 5 folding operating tables and a portable field x-ray unit, surgical equipment and drugs. It weighs approximately 14 tons, occupies approximately 2000 cubic feet of storage space and is composed of 450 separate packages, which can be transported in a single van. Sufficient expendable medical supplies are stored with this unit to enable continuous operations for forty-eight hours during a disaster. The total cost of a 200-bed improvised hospital unit is $26,500. When installed in a public building such as a school or gymnasium, this hospital would include the following items: triage room, shock-treatment ward, 3 operating rooms, sterilizing room, central supply room, pharmacy, laboratory and x-ray plant capable of producing sixty-second x-ray films with its own portable generator and transformer.

To ascertain the optimum distribution for 200-bed hospitals of this kind, studies are being made of population density and the location of critical target areas. In this way cardinal principles of mobility and dispersal in planning for medical civil defense will be adhered to so that the greatest possible utility will be derived from this unit. The 200-bed hospital unit is the result of a prolonged survey conducted by hospital and medical personnel of the armed forces and Civil Defense authorities at Hiroshima and Nagasaki. It is hoped that in this way a system can be developed for establishing emergency hospitalization for casualties in any large-scale disaster.

The 200-bed improvised emergency hospital unit can be effectively utilized in a large-scale natural disaster such as a tornado or hurricane to supplement any existing hospital needs. A manual of procedures that will be developed in co-operation with the Massachusetts Medical Society will outline the staff organization and operation of this hospital unit. Plans are now being made to organize training and demonstration programs that will be of assistance to the physician. Thus, it will be possible, through timely planning, to have immediately available emergency hospital facilities and equipment that physicians may urgently need in the event of a disaster.

THOMAS F. MAHER, M.D., D.P.H.
*Executive Medical Officer*

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## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

| Orthopedic Clinic | Date | Clinic Consultant |
|---|---|---|
| Salem | January 3 | Paul W. Hugenberger, M.D. |
| Gardner | January 4 | Carter R. Rowe, M.D. |
| Haverhill | January 5 | William T. Green, M.D. |
| Greenfield | January 6 | Charles L. Sturdevant, M.D. |
| Lynn* | January 10 | Daniel M. Killoran, M.D., and John J. Crowley, M.D. |
| Brockton | January 13 | George W. Van Gorder, M.D. |
| Lowell | January 14 | Albert H. Brewster, M.D. |
| Worcester | January 14 | John W. O'Meara, M.D. |
| Fall River | January 17 | David S. Grice, M.D. |
| Springfield | January 18 | James D. Fisher, M.D. |
| Pittsfield | January 19 | Edward J. Coughlin, Jr., M.D. |
| Hyannis | January 20 | Paul L. Norton, M.D. |

| Rheumatic-Fever Clinic | Dates |
|---|---|
| North Reading | January 4, 11, 18, 25 |
| Fitchburg | January 5, 12, 19, 26 |

| Plastic Clinic | Held | Consultant |
|---|---|---|
| Eastern Massachusetts | Semi-monthly | Bradford Cannon, M.D. |
| Western Massachusetts | Monthly | Joseph M. Baker, M.D. |

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

## BOOKS RECEIVED

**The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.**

*Die zentralnervösen Wirkungen von Heilmitteln.* By E. Rothlin. 8°, paper, 59 pp., with 7 illustrations and 2 tables. Stuttgart: Georg Thieme, 1953. DM 2.40 ($0.60). (Distributed by Intercontinental Medical Book Corporation, New York.)

This small monograph discusses the clinical and experimental action of drugs on the central nervous system. There are illustrations, one of which is a picture of the first operation under ether at the Massachusetts General Hospital in 1847. The portrayal is incorrect in a minor detail: the small tumor should be on the left side of the neck and not on the right.

*Neurosenfrage, Ursachenbegriff und Rechtsprechung.* By Dr. W. Schellworth, Berlin. Second edition. 8°, paper, 98 pp. Stuttgart: Georg Thieme, 1953. DM 9.- ($2.06). *(Arbeit und Gesundheit,* Neue Folge Heft 53.) (Distributed by Grune and Stratton, New York.)

The first edition of this special monograph on the neuroses and their relation to industrial occupations was published in 1939. This new edition has been revised and enlarged. The material is divided into three main parts: the

question of neuroses, the causative factors and legal aspects. A short bibliography is appended to the text.

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*Klinische Darmbakteriologie: Für die ärztliche Praxis.* By Prof. Dr. med. et phil. Tr. Baumgärtel, München. 8°, paper, 130 pp. Stuttgart: Georg Thieme, 1954. DM 14.40 ($3.40). (Distributed by Intercontinental Medical Book Corporation, New York.)

This monograph deals with the clinical bacteriology of the intestines. The text is divided into two parts: general and special. The general discusses the bacterial flora and their metabolism. The special deals with the clinicobacteriologic diagnosis; the pathological variability of the intestinal flora; causation and pathology; and treatment of nonspecific disturbances of the intestines. The pertinent literature is surveyed, and there are indexes of authors and subjects.

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*Alcoholism.* By Jackson A. Smith, M.D., director of the alcoholic clinic, Jefferson Davis Hospital, assistant professor of psychiatry, Baylor University College of Medicine, Houston, Texas, diplomate of the American Board of Psychiatry and Neurology, and member of the staffs of Jefferson Davis, Methodist, Hermann, Houston Tuberculosis and Southern Pacific hospitals. 12°, cloth, 72 pp. Philadelphia: J. B. Lippincott Company, 1954. $3.00.

This primer presents the latest knowledge on the treatment of chronic alcoholism, including the Antabuse reaction. Originally published in *American Practitioner and Digest of Treatment* for 1953, the material is reprinted in compact form.

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*Grenz Ray Therapy: Principles, methods, clinical applications.* By Gustav Bucky, M.D., clinical professor of dermatology emeritus, New York University College of Medicine; and Frank C. Combes, M.D., professor of dermatology and syphilology, New York University Postgraduate Medical School, and director of dermatology and syphilology, Bellevue Hospital. 8°, cloth, 204 pp., with illustrations. New York: Springer Publishing Company, 1954. $8.50.

This new book on a new field of radiotherapeutics — the borderline electromagnetic rays — is divided into two main parts: the principles and the practice of the therapy. The section on practice discusses the technic of the treatment and its use in skin, tropical and oral diseases and in ophthalmology. The text is written by nine authors. Lists of references are appended to the chapters, and there is a classified bibliography of 20 pages. There is a good index, and the publishing is excellent. The book should be in all collections on radiology.

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# NOTICES

## NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be presented by the Peter Bent Brigham Hospital and invited speakers from New England at Morse Auditorium, Museum of Science, Boston, on January 3, 1955, at 8 p.m. The program is as follows:

Peter Bent Brigham Hospital. Dr. Samuel A. Levine, presiding.

Vectorcardiography in the Detection of Combined Ventricular Hypertrophy. Drs. Gerald H. Whipple and Harold D. Levine.

Sympathectomy for Arteriosclerosis: Status of one hundred patients five or more years after operations. Drs. Edward A. Edwards and Chilton Crane.

Some Observations on Complete Heart Block. Drs. George B. Penton, Harold Miller and Samuel A. Levine.

Speakers from New England. Dr. Edward F. Bland, presiding.

Nor-epinephrine and Epinephrine Content of Normal and Diseased Human Hearts. Drs. W. Raab and W. Gigee, University of Vermont.

The Surgical Treatment of Aortic Stenosis. Dr. W. B. Neptune, New England Deaconess Hospital, Boston.

Surgical Treatment of Coronary Insufficiency. Dr. R. Adams, Huggins Hospital, Wolfeboro, New Hampshire.

Interested physicians and medical students are invited.

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## NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held at the Yale–New Haven Medical Center, New Haven, Connecticut, on February 4, 1955.

The program is as follows:

8:00 a.m.-12:00 m. Operative schedule and demonstrations. Grace–New Haven Community Hospital. Hospital of St. Raphael.

2:00-2:20 p.m. (Entire afternoon session to be held at Brady Auditorium, Yale University School of Medicine.) Use of Succinylcholine during Endotracheal Extubation: oximetric and electrocardiographic observations. Drs. R. S. Lambie and Frank Pfaff, Hospital of St. Raphael.

2:30-3:10 p.m. Some Autonomic Reactions Evoked by Cerebral Stimulation in the Conscious Monkey. Dr. José M. Delgado, Yale University School of Medicine.

3:20-3:50 p.m. Observations on Neuromuscular Function in the Anesthetized Patient. Dr. R. T. McSherry, Grace—New Haven Community Hospital.

4:30-5:30 p.m. Refreshments at the Quinnipiack Club.

5:30-7:00 p.m. Dinner at the Quinnipiack Club.

7:00-7:30 p.m. Business meeting at the Quinnipiack Club.

7:30-9:00 p.m. Breathing Mechanics and Pulmonary Ventilation during Anesthesia. Dr. Donald F. Proctor, Johns Hopkins University School of Medicine.

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## HOUSE OF GOOD SAMARITAN RESIDENCY

The position of chief resident physician at the House of the Good Samaritan (Children's Medical Center), Boston, Massachusetts, will be available on July 1, 1955. The resident physician will work closely with members of the research and clinical staffs, will have an opportunity to participate in clinical research projects and the teaching activities of the hospital and will receive a teaching appointment at Harvard Medical School. The salary is $3000 (if single) or $3600 (if married) a year, and board, room and laundry are provided. Information may be obtained from Miss Elma Hussey, Superintendent, House of the Good Samaritan, 25 Binney Street, Boston 15, Massachusetts.

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## HARVARD SCHOOL OF PUBLIC HEALTH SCHOLARSHIPS

Harvard School of Public Health announces that scholarships are available for postgraduate education for the degrees of Master of Public Health, Doctor of Public Health, Master of Science in Hygiene, Doctor of Science in Hygiene and Master of Industrial Health to applicants in the following fields: physicians, dentists and veterinarians; industrial physicians; public-health nurses; social workers; health educators; and other college graduates who have concentrated in one of the natural sciences or the environmental aspects of engineering.

Further information may be obtained from the secretary, Harvard School of Public Health, 55 Shattuck Street, Boston 15, Massachusetts. Applications must be received before March 1, 1955.

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## POSITIONS AT SAINT ELIZABETHS HOSPITAL

The United States Civil Service Commission announces that applications are being accepted for Medical Officer to fill trainee positions at Saint Elizabeths Hospital, Washington, D. C. Appointments will be open July 1, 1955, for rotating intern at $2800 and resident-in-training in psychiatry and in neurology at $3400 to $4200 a year.

Applicants for the intern positions must be fourth-year students in an approved medical school. Applicants for the

resident positions must be graduates of an approved medical school with the degree of doctor of medicine and in addition must have completed a full year of internship or now be serving it. No written test is required. The age limit of thirty-five years will be waived for persons entitled to veteran preference. Full details are given in Examination Announcement No. 429(B).

Applications will be accepted by the Board of Civil Service Examiners, Saint Elizabeths Hospital, Washington 20, D. C., and forms may be obtained from post offices or from the United States Civil Service Commission, Washington 25, D. C.

## MID-WINTER RADIOLOGIC CONFERENCE

The Mid-Winter Radiologic Conference, sponsored by the Los Angeles Radiological Society, will be held at the Ambassador Hotel, Los Angeles, California, on February 26 and 27, 1955. The program is as follows:

Renal Angiography. Tolerance to Contrast Mediums. Prof. Olle Olsson, Lund, Sweden.

Neoplasms of Bone. Fibrous Dysplasia of Bone. Dr. Paul C. Hodges, Chicago, Illinois.

*Hodgkin's Disease. Palliation and Care of Terminal Patients.* Dr. Simeon Cantril, Seattle, Washington.

Medical Isotopes. Dr. Leslie Bennett, Los Angeles, California.

Value of Posteroanterior Chest Film in Cardiac Radiology. Dr. George Jacobson, Los Angeles, California.

Tumors of the Small Intestine. Physical Problems in Detection of Cancer of the Stomach. Dr. Ross Golden, Los Angeles, California.

The Pulmonary Cripple. Dr. Charles E. Grayson, Sacramento, California.

Hotel reservations should be made through the convention manager, Ambassador Hotel, Los Angeles, California, and further information may be obtained from Dr. Richard A. Kredel, 65 North Madison Avenue, Pasadena, California.

## AMERICAN COLLEGE OF CHEST PHYSICIANS AWARD CONTEST

The Council on Undergraduate Medical Education of the American College of Chest Physicians offers three cash awards of $250, $100 and $50 each to be given annually for the best contribution, prepared by any undergraduate medical student studying for a degree in medicine, on any phase of the diagnosis and treatment of chest diseases, including heart and lungs.

Applicants are requested to study the format of *Diseases of the Chest* for length, form and arrangement of illustrations, observing the following conditions: 5 copies of the manuscript typewritten double spaced in English must be submitted to the executive director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois before April 10, 1955; a motto or other device must be affixed to the title page and to a sealed envelope that encloses the name and address of the author; and a letter from the dean or chairman of the department of medicine must be included, certifying that the author is a medical student studying for the degree in medicine.

Awards will be announced at the annual meeting of the American College of Chest Physicians in Atlantic City, New Jersey, June 2-5, 1955.

## AMERICAN PHARMACEUTICAL ASSOCIATION AWARD

Nominations are being received by the American Pharmaceutical Association for the 1955 Chilean Iodine Educational Bureau Award of $1000 recognizing outstanding research in the chemistry and pharmacy of iodine and its compounds as applied to pharmacy or medicine.

Any member of the American Pharmaceutical Association may propose a nominee by submitting 8 copies of each of the publications to be considered in the competition, a biographic sketch including date of birth and a list of the nominee's publications and 8 copies of the nomination to Robert P. Fischelis, Secretary, American Pharmaceutical Association, 2215 Constitution Avenue, N.W., Washington 7, D. C., before January 1, 1955.

Nominees must be residents of the United States or Canada, must have accomplished outstanding research in the chemistry or pharmacy of iodine and its compounds and shall have been engaged in, completed or published reports on investigations for which the award is made.

## SOCIETY MEETINGS AND CONFERENCES

DECEMBER, 1954–APRIL, 1955. Postgraduate Medical Institute. Page 451, issue of September 9.

DECEMBER, 1954–MAY, 1955. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

DECEMBER 23–29. Consultation Clinics for Crippled Children in Massachusetts. Page 918, issue of November 25.

DECEMBER 29. Lahey Clinic Lectures. Page 993, issue of December 9.

JANUARY 3–MAY 9, 1955. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

JANUARY 3. New England Cardiovascular Society. Page 1075.

JANUARY 3–26. Consultation Clinics for Crippled Children in Massachusetts. Page 1074.

JANUARY 3–17. Hartford Medical Society. Page 496, issue of September 16.

JANUARY 4 and 18, FEBRUARY 1 and 15. New England Deaconess Hospital Lectures. Page 993, issue of December 9.

JANUARY 7–MARCH 25. Postgraduate Course in Occupational Medicine. Page 922, issue of November 25.

JANUARY 8–MAY 7. Middlesex South District Medical Society. Postgraduate Course. Page 758, issue of October 28.

JANUARY 10–15. Course in Care of Atomic Casualties. Page 285, issue of August 12.

FEBRUARY 4. New England Society of Anesthesiologists. Page 1075.

FEBRUARY 4 and APRIL 8. Massachusetts Society for Research in Psychiatry. Page 679, issue of October 14.

FEBRUARY 7–9. McIntyre-Saranac Conference. Page 410, issue of September 2.

FEBRUARY 11–25. Pan-American Academy of General Practice. Page 496, issue of September 16.

FEBRUARY 26 and 27. Mid-Winter Radiologic Conference. Notice above.

FEBRUARY 28–MARCH 2. American Orthopsychiatric Association. Page 994, issue of December 9.

MARCH 7–12. Course in Care of Atomic Casualties. Page 285, issue of August 12.

MARCH 23–26. International Academy of Proctology. Page 876, issue of November 18.

APRIL 21 and 22. New York Academy of Medicine (Eastern States Health-Education Conference). Page 922, issue of November 25.

MAY 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.

JUNE 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.

JUNE 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

## CALENDAR FOR THE WEEK BEGINNING THURSDAY, DECEMBER 30

THURSDAY, DECEMBER 30

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m. Mortality and Morbidity Meeting. St. Margaret's Hospital, Dorchester.

*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

FRIDAY, DECEMBER 31

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*(Concluded on page xvii)*

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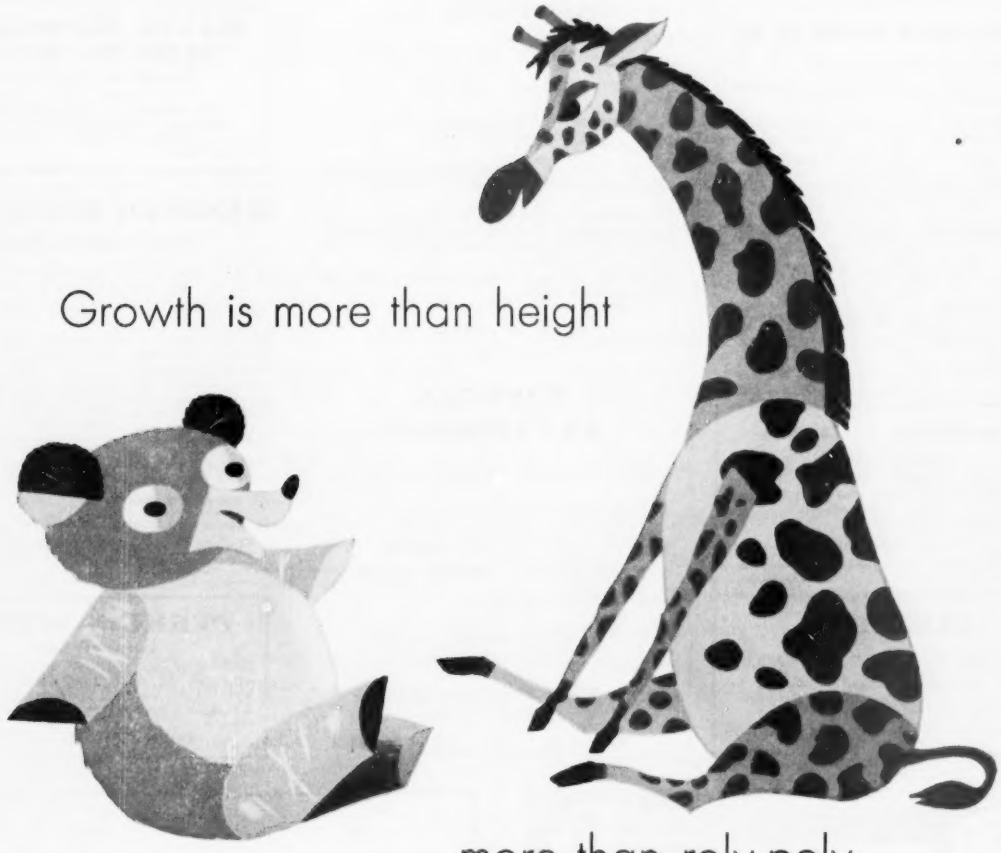

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*(Concluded from page 1076)*

*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, JANUARY 1
Holiday

MONDAY, JANUARY 3
Hartford Medical Society. Annual Meeting. The Value of a Sense of Humor. Samuel Ramsay. Hunt Memorial Building, Hartford.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Drs. MacMahon and Baty. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–8:00 p.m. Pathology Conference. Dr. MacMahon and Staff. Stearns Auditorium, New England Center Hospital.
*8:00 p.m. New England Cardiovascular Society. Morse Auditorium, Museum of Science, Boston.

TUESDAY, JANUARY 4
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Combined Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Drs. Patterson, MacMahon and guest. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. New England Deaconess Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*5:45 p.m. New England Deaconess Hospital Lecture. Benign and Malignant Skin Tumors. Dr. Robert Tilly. Joslin Amphitheater, New England Deaconess Hospital.

WEDNESDAY, JANUARY 5
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. Sullivan, B. Selverstone and Hope. Stearns Auditorium, New England Center Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. Out-Patient Department.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

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1. Co Tui, Minutes of the Conference on Metabolism, Aspects of Convalescence, Including Bone and Wound Healing. Josiah Macy, Jr., Foundation, 5th Meeting, Page 57, 1943.

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